Unit : Bovine Mastitis
Lesson : 4

Treatment of Mastitis

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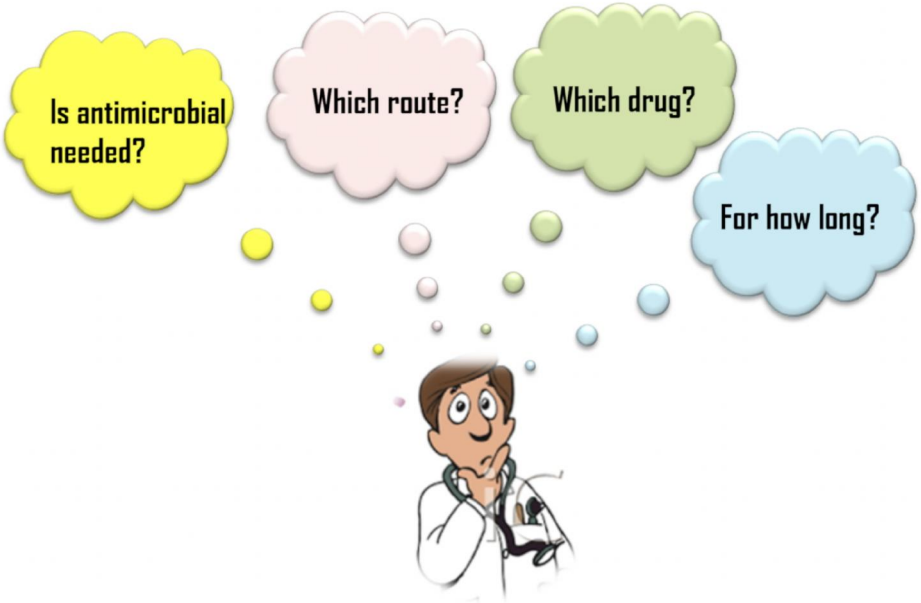
Treatment of Mastitis

- Principle of treatment
- Antibiotic therapy
- Antimicrobial resistance
- Non-antibiotic Therapy

Treatment strategy



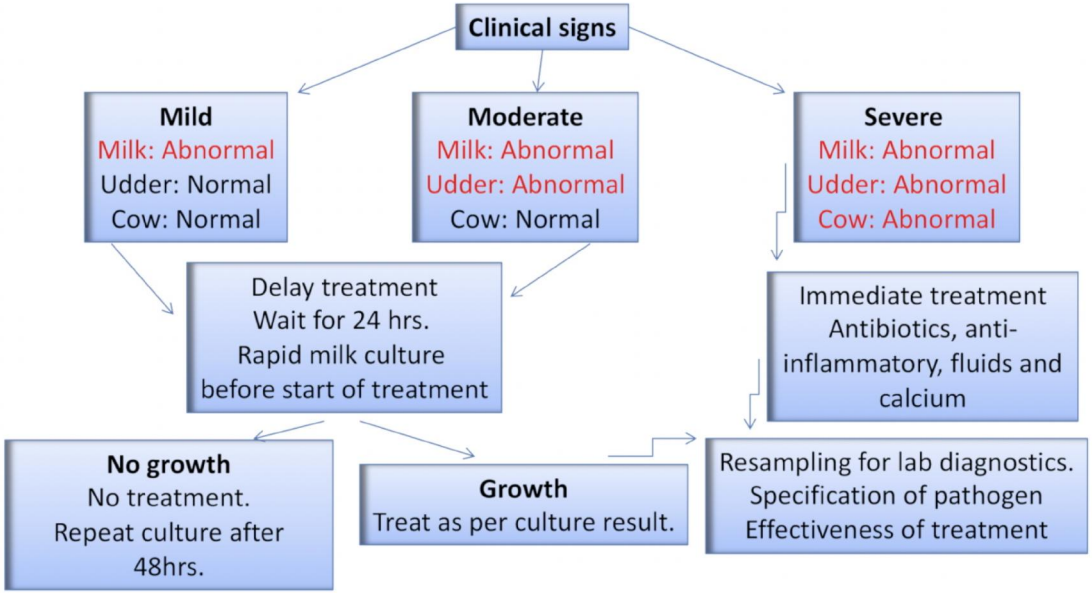
Therapy decision (Antimicrobial / Supportive?)

Factor	Good response	Poor response	Variable response
Pathogen	S.agalacteae	S.aureus	Environmental pathogens
Enzyme level		High NAGase	
Duration	Acute cases	Chronic (Esp S.aureus)	
Stage of lactation	Late lactation (not economical)		Other stages of lactation
Age	Young cows		

Cows in a herd with mild clinical mastitis due to environmental pathogens return to normal in 5-6 milking without any treatment.

Treat cases with gram positive mastitis for 2 days; observe for mild cases with gram negative or culture negative.

Radostits, 2017; Sharun et al., 2021


Clinical signs
Mild
Milk: Abnormal
Udder: Normal
Cow: Normal
Moderate
Milk: Abnormal
Udder: Abnormal
Cow: Normal
Severe
Milk: Abnormal
Udder: Abnormal
Cow: Abnormal
Delay treatment
Wait for 24 hrs.
Rapid milk culture
before start of treatment
Immediate treatment
Antibiotics, anti-
inflammatory, fluids and
calcium
No growth
No treatment.
Repeat culture after
48hrs.
Growth
Treat as per culture result.
Resampling for lab diagnostics.
Specification of pathogen
Effectiveness of treatment

Choice of Antimicrobial agent

Culture and sensitivity

Previous case studies

Antibiotic sensitivity differs from place to place and pathogen to pathogen

Do not wait 2 days for getting culture result for choosing antibiotic to treate a clinical case

Response to therapy may differ from invitro and invivo (microabscesses and biofilm formation)

Antibiotics are distributed unevenly in an inflamed gland.

Efficacy of antibiotic following intramammary administration is governed by factors like lipid solubility, tissue protein binding, pH and presence of inflammatory exudates (Malik et al., 2004).

Frequency and duration of treatment

Fluoroquinolones and aminoglycosides	**Concentration dependent**
Macrolides, β-lactams, and lincosamides	**Time dependant**
Extended or aggressive antimicrobial therapy for 5 to 8 days is more effective in treating intramammary infections than label intramammary therapy of 2–3 days.	
Higher than normal recommended dose is required to achieve better therapeutic level of antimicrobial	

Pathogen	Milk	Udder	Cow	Therapy
S.aureus Chronic	Occasional clots, watery	Gradual induration	-	Less effective; intramammary
Acute/ peracute	Thick clots, pus	Acute swelling, gangrene	Fever, anorexia, ruminal stasis, recumbency	Trimethoprim-sulfonamide, Penicillins, electrolytes, oxytocin
Coliforms -peracute	Watery to yellow thin serous, small flakes	Swollen, warm, erythema, pain	Anorexia, fever, cold extremity, diarrhoea, recumbency, tachycardia	Cephalosporins, quinalones, OTC, IV fluid, electrolytes, NSAIDs, intramammary
Coliform-acute	Watery to serous, flakes	swollen	Varying signs	
S.agalactiae	Clots in watery fore milk. Milk yield normal after treatment.	Swollen, hot –initially. Induration at teat cistern and lower udder- later	Febrile and off feed- rare	Very sensitive to intramammary therapy with penicillin and cephalosporins.
Corynebacterium bovis	Thicker milk than normal	Large, firm - rarely	-	As above
Mycoplasma spp	Initial-Apparently normal, depositing on collected milk. Later- scanty. Cheesy, bloody, purulent. No big clots	Multiple quarter or all qtrs, Gross swelling,	Sudden onset in many cows. No or mild systemic signs usually. Swollen mammary LN. Arthritis of knee/fetlock	Poor response. Remains infected lifelong. Intramammary aggrevates the disease.
T.Pyogenes *Summer mastitis*	Initial-watery, clots Later-purulent, putrid odour	Usually front qtr, swollen, very hard and sore. Severe thelitis, thickening, obstruction.	Fever, anorexia, tachycardia, Fly H.irritans (horn fly) seen. Abortion or fetal growth retardation	Poor response. Sulfadimidine/ OTC with broad spectrum IM infusion/ rendering non nonfunctional

Dry cow therapy

Dry cow therapy aimed to extinguish existing IMIs and control the new infections during the dry period (Derakhshani et al. 2018).

Internal teat sealant (ITS) when used in combination with antibiotic dry-cow therapy significantly reduced the SCC along with improved prevention of subclinical mastitis (Golder et al. 2016).

- using Weissella cibaria, a lactic acid bacterium
- bismuth subnitrate and chlorhexidine

Dry cow therapy

- Blanket Vs Selective dry cow therapy
- Effective in treating S.aureus and S.agalactiae infections
- Slow release Cloxacillin and Cephalosporins may be preferred.
- Intramammary infusion, 10-12 weeks before parturition in heifers.

Anti – inflammatory and Supportives

Non-steroidal anti-inflammatory drugs resulted in lower SCC, reduced milk yield losses, improved clinical outcomes, and reduced culling rates as compared with antibiotic therapy alone (McDougall et al. 2009b)

NSAIDs are better when compared to corticosteroids in ameliorating systemic abnormalities (Radostits, 2017)

Large volumes of isotonic crystalloid fluids can be rapidly administered under pressure at 0.5 L/ min through a 12-gauge catheter.

Administration of hypertonic saline immediately followed by access to drinking water.

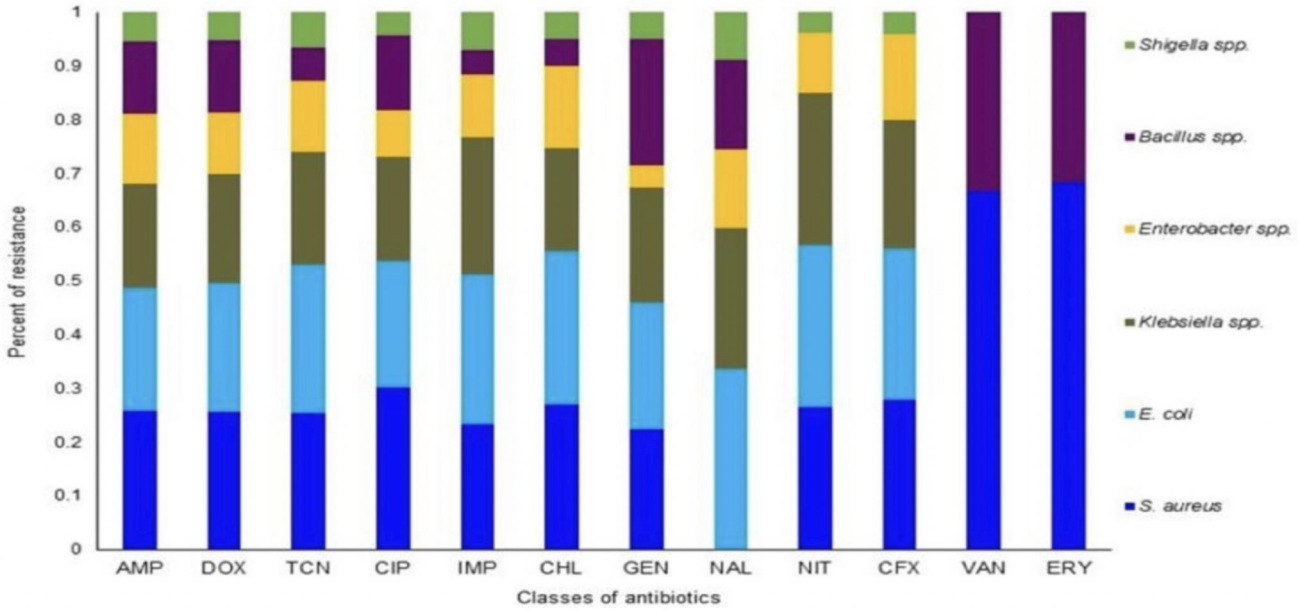
Anti inflammatory and Supportives

Oxytocin 10-20 units im

- Supports milk removal from infected mammary quarters also clears non S.aures pathogens from udder.
- Causes increased somatic cell counts (SCC) in milk and enables the transfer of immunoglobulins (Ig) from blood into milk through a reduced blood-milk barrier integrity (Strasser et al., 2021)

Failure to therapy

- The presence of microabscesses and inaccessibility of the drug to the pathogen
- Ineffective drug diffusion
- Inactivation of the antimicrobial by milk and tissue proteins
- Inefficient killing of the bacteria and intracellular survival of bacteria
- Increased antimicrobial resistance



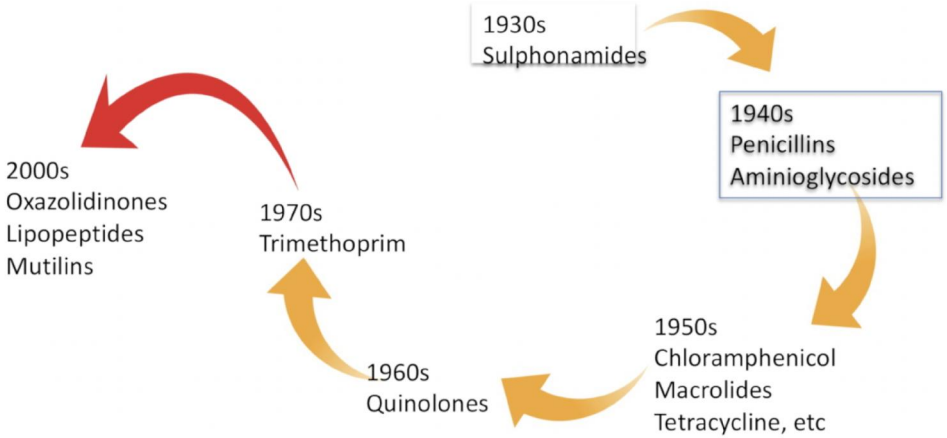
Antibiotic resistance pattern of bovine clinical mastitis pathogens

AMP, Ampicillin; DOX, Doxycycline; TCN, Tetracycline; CIP, Ciprofloxacin; IMP, Imipenem; CHL, Chloramphenicol; GEN, Gentamycin; NAL, Nalidixic acid; NIT, Nitrofurantoin; CFX, Cefoxitin; VAN, Vancomycin; ERY, Erythromycin (Hoque et al., 2020)

Antimicrobial resistance...

- Multidrug resistance might be associated with
- unethical overuse of antibiotics in dairy animals (Preethirani et al., 2015; Curone et al., 2018; Tomazi et al., 2018; Cheng et al., 2019; Zaheer et al., 2019), and
- extensive application of toxic chemicals and metals in agricultural use (Reyes-Jara et al., 2016; Vaidya et al., 2017), or
- might have a function in the gut microbiome that is still unknown (Penders et al., 2013; Hu et al., 2014b; Ciesinski et al., 2018).

Antibiotic milestones / Antimicrobial resistance



who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Enterobacteriaceae include: Klebsiella pneumonia, Escherichia coli, Enterobacter spp., Serratia spp.,
Proteus spp., and Providencia spp, Morganella spp.

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

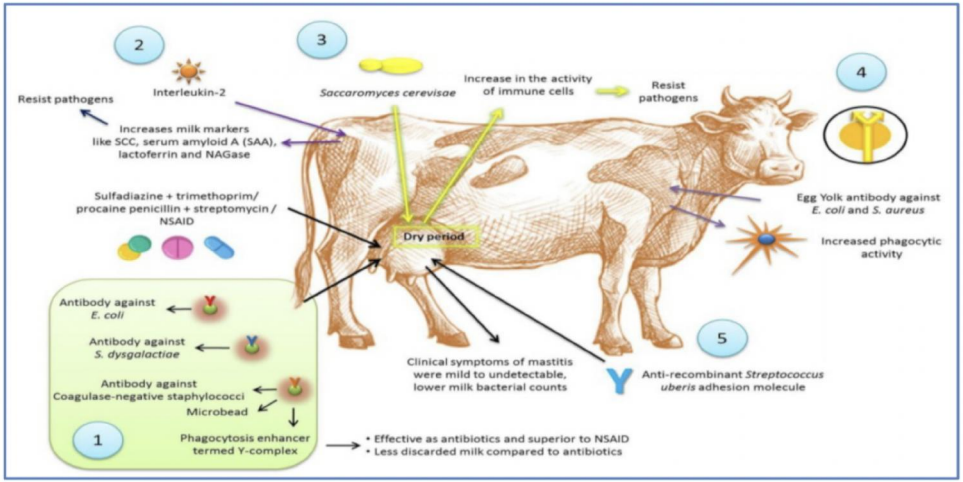
Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

Non-antibiotic therapy

- Immunotherapy, Nanoparticles, nutraceuticals, herbal extracts, probiotics, laser radiation, lysozymes, saponin, propolis, lysosubtilin, antibacterial peptides and the intramammary infusion of lactoferrin or ozone in addition to traditional medicine to manage antimicrobial resistance (Malinowski et al. 2019).

Immunotherapy



1. Microbeads carrying specific antibodies, 2. Interleukin-2 injection, 3. Infusion of extract of Saccharomyces cerevisae yeast, 4. Specific IgY from egg yolk, 5. Use of anti-recombinant Streptococcus uberis adhesion molecule.

Nanoparticles

- Nanoparticle-based therapeutic techniques like liposomes, nanogels, polymeric nanoparticles, inorganic nanoparticles, and solid lipid nanoparticles are gaining popularity as excellent tools for managing S. aureus mastitis (Algharib et al. 2020).

- Honey, when used along with gold nanoparticles produced significant in vitro anti-microbial activities against methicillin- resistant (MRSA) and vancomycin-resistant (VRSA) coagulase-positive S. aureus mastitis strains (Omara 2017).

- Gold nanoparticles were superior to silver nanoparticles (Elbehiry et al.2019).

Nanoparticles

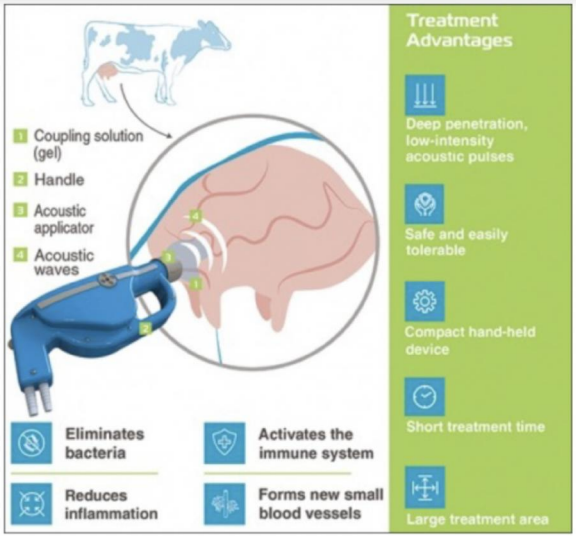
- Nanosized emulsions of soya bean oil shows a potent antimicrobial effect even against multidrug-resistant pathogens (El- Sayed and Kamel 2019b)
- Intramammary infusion of nanosilver cream and ceftiofur has a therapeutic efficiency of up to 93.33% of the cases (Chau et al. 2019).
- Chitosan nanoparticles (Ch-NPs) are reported to have great therapeutic potential for bovine mastitis (Orellano et al. 2019).
- Nanoformulation of curcumin can improve its oral bioavailability and can act by reducing the pro-inflammatory mediators in S. aureus infected mammary tissue mouse model (Suresh et al. 2018).

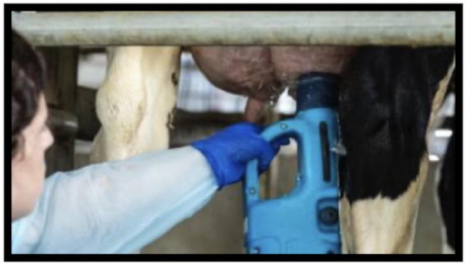
Photodynamic therapy

- By release of nascent oxygen and the formation of hydroxide radicals (i.e., convert oxygen to reactive oxygen species (ROS) compounds) inside the target tissues through photosensitization of certain nano-compounds (e.g., safranine-O photosensitizer).

- The oxygen and hydroxide radicals kill the present bacteria selectively and overcome the problem of antibiotic resistance (da Silva Junior et al. 2019,Scholte2019).

Acoustic pulse therapy (APT), also referred to as low-intensity shockwave (SW) treatment





Radiation therapy

Radiation therapy

- Radiation of the inflamed udder tissue with low-intensity laser in combination with antibiotic
- Improve their regenerative capacity, reduce pain and inflammation and enhance the phagocytic activity of milk granulocytes (Malinowski, et al. 2019).

Electrolyzed oxidizing water

- The activation of normal water takes place by electrolysis of NaCl solution to produce hypochlorous acid (HOCl) and sodium hydroxide.
- Both compounds own antimicrobial properties and can be applied in the dairy industry as disinfectants (Kaoud 2015).

Stem cell therapy

- Mesenchymal stromal cells of adipose tissue have
  - anti-inflammatory,
  - antimicrobial, and
  - immunomodulatory properties via the activation of innate immunity (Lange-Consiglio et al. 2019; Yuan et al. 2014; Cahuascanco et al. 2019; Singh et al., 2020).
- Stem cells from adipose tissue have
  - high angiogenesis capacity which is needed for the regeneration of highly vascular udder tissues (Costa et al. 2019).

Alternatives to antibiotics- Probiotics

Source	Application site	Mechanism of action	References
Corynebacterium bovis	*In vivo* (a cow model)	An increase in somatic cell count and a reduction in the percentage of infection	Brooks and Barnum (1984)
Lactococcus lactis DPC3147	*In vivo* (a cow model)	A rapid influx of neutrophils that enhanced the immune response against *Staphylococcus aureus*	Klostermann *et al.* (2008)
Lactobacillus plantarum ATCC 8014	*In vitro*	Antimicrobial activity against *S. aureus* (production of inhibitory compounds such as hydrogen peroxide)	Soleimani *et al.* (2010)
Pediococcus pentosaceus CRL1831 *Weissella cibaria* CRL1833 *Enterococcus hirae* CRL1834 *Enterococcus hirae* CRL1835	*In vitro*		Espeche *et al.* (2012)
Lactobacillus perolens CRL 1724	*In vitro* on cell line		Frola *et al.* (2012)
Lactobacillus casei	*In vitro* on cell line	Reduction of *S. aureus* adhesion and internalization into bovine mammary epithelial cells (coaggregation, and inhibition of the expression of major virulence regulators)	Bouchard *et al.* (2013)
Lactococcus lactis V7	*In vitro* on cell line		Assis *et al.* (2015)
Lactobacillus paracasei subsp. Paracasei *Lactobacillus plantarum*	*Ex vivo* (cells from freshly udders) and *in vitro*	Antimicrobial activity against *S. aureus* (secretion of antimicrobial substances and modulation of the cow's immune response)	Diepers *et al.* (2017)
Lactobacillus lactis subsp. lactis CRL1655 *Lactobacillus perolens* CRL1724	*In vivo* (cow model)	Simulation of the immune response of the cow by triggering the production of specific antibodies (recommended at the dry-off period)	Pellegrino *et al.* (2017)
Lactobacillus rhamnosus ATCC 7469 *L. plantarum* 2/37 *L. brevis* 104/37 *L. plantarum* 118/37 *L. plantarum* 6E	*In vitro*	Disruption of *S. aureus* biofilms	Wallis *et al.* (2019)

Bacteriocins

- Antimocrobial peptides + Antibiotics = Synergism (Chung and Khanum 2017).
- The AMPs of multicellular organisms such as defensins and cathelicidins play major role in the innate immunity of vertebrates
- AMPs of unicellular organisms like bacteriocins suppress competitor species (Sang and Blecha 2008) stimulate angiogenesis, produce chemokines, accelerate wound healing process, and influence apoptosis in multicellular organisms (Moravej et al. 2018).
    - Limitations- short half-life, high production cost, enzymatic degradation, and cytotoxic effects on the eukaryotic cells (Moravej et al. 2018).

Bactriophage

- Bactriophage cocktail therapy is used instead of single phage
- Host-specific in opposite to antibiotics, which also kill beneficial gut bacteria (Sayed and Kamel., 2021).
- Injection of phage endolysins (enzymes responsible for bacterial cell lysis) was more effective than bacteriophages but resistance development was very fast (Angelopoulou, et al. 2019)

Completely drying the quarter

- 30 to 60 mL of 3% silver nitrate solution
- 20 mL of 5% copper sulfate solution
- 100 to 300 mL of 1 : 500, or 300 to 500 mL of a 1 : 2000 acriflavine solution
- 120 mL of 5% povidone iodine solution (0.5% iodine)
- Three daily infusions of 60 mL of chlorhexidine

Thank you