Review Article

Topical Antimicrobial Therapy: Current Status and Challenges

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Abstract

Topically applied antibacterial agents are widely used. Opinions regarding the clinical efficacy of topical antibiotics are conflicting, and for most indications, alternative oral therapies are available. Topical application has many potential advantages over systemic therapy that includes high and sustained concentrations of drug directly at the infected site, low quantity of antibiotic needed, better compliance, fewer systemic side effects and potentially less chance of antimicrobial resistance. Despite these advantages, an important concern has been the difficulty in monitoring antibiotic dosage and duration of therapy. Most topical preparations are applied on sites with pre-existing normal bacterial flora, and the detrimental effect of antibiotic on the 'good' bacteria is difficult to control. Unnecessary exposure of the resident microflora to high drug levels may select drug-resistant phenotypes. The number of antibiotics available and the quality and composition of the formulations recommended for topical drug delivery are improving. Their role in the prevention and treatment of locally invasive infections is established for many clinical conditions. However, there is still a lacuna in the availability of pharmacokinetic (PK) knowledge of these topical preparations and translation of the same to clinical practice. In addition, reporting the clinical outcome following the use of these agents and its analysis considering the recently proposed epidemiological cut-off value-based cut-offs are also areas which merit further research. In this review, we highlight the clinical utility and the PK aspects of topical antimicrobials in various infections. We also discuss the limitations of the current antimicrobial susceptibility testing (AST) protocols and new methods for AMST for topical agents.

Keywords: Antimicrobial susceptibility, drug formulation, pharmacokinetics, topical antimicrobials

Introduction

Even with multiple systemic antibiotics available, topically applied compounds are widely used. In comparison to systemic therapy, topical application has various potential advantages that include high and sustained concentrations of drug directly at the infected site, low quantity of antibiotic needed, better compliance, fewer systemic side effects and potentially less chance of antimicrobial resistance.[1]

Despite these benefits, however, few agents have been effective in clinical trials. In addition, they may possibly alter the normal flora interfering with wound healing and are difficult to dose and test for antimicrobial susceptibility. Frequently, it is assumed that topical preparations concentrate at the infection site. However, for most topical agents, abetting pharmacological data such as actual concentrations and factors affecting it are largely unknown. In this review, we highlight the clinical utility and the PK aspects of topical antimicrobials in various infections. We also discuss the limitations of the current antimicrobial susceptibility testing (AMST) protocols and new methods for AMST for topical agents.

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Clinical Use of Topical Antimicrobial Agent

Opinions regarding the clinical efficacy of topical antibiotics are conflicting, and for most indications, alternative oral therapies are available. However, in view of the rising antimicrobial resistance and due to the targeted availability of drug at the intended site, the use of topical antibiotic therapy is still prevalent in clinical practice. A summary of the various topical antimicrobials and their clinical utility for common infections is shown in Table 1.

Skin infections, burns and wound care

As the microcirculation in wounded skin, especially in burns, is more or less destroyed, oral or systemic antibiotics are

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Table 1: Summary of the clinical utility of commonly used topical antimicrobial agents for skin, ear and eye infections

Drug	Skin infection	Formulation	Dosage	Comments
Mupirocin	SSTI, nasal carriage of MRSA, impetigo, burn wound care	2% cream/ ointment	2-3 times daily for 10 days (MRSA nasal clearance normally after 5-7 days)	It is a mixture of pseudomonic acids produced by submerged fermentation of *P. fluorescens* Pregnant and lactating women should use it with caution Ointment base containing polyethylene glycol should be avoided in patients with very large surface lesions or renal impairment due to renal toxicity from this component Use for >10 days avoided to prevent bacterial resistance
Neomycin	SSTI	0.5% cream	Up to three times daily; short-term use	Aminoglycoside produced from fermented *Streptomyces fradiae* Contact allergy is a common side effect and over-the-counter use increases the risk of sensitisation Hearing loss, especially in patients with renal impairment, is reported Available as combination with bacitracin, neomycin and polymixin called neosporin
Silver sulfadiazine	Burn wound care	1% cream	Twice a day to a topical thickness of 1.6 mm	Silver concentration should be monitored in the blood and/or urine especially in patients with large burns, renal and hepatic impairment, and the prolonged and extensive use Avoided in patients with allergy to sulpha drugs and glucose-6-phosphate dehydrogenase deficiency Avoided in pregnant and lactating women (causes kernicterus)
Bacitracin-zinc	Skin/wound infection Burn wound care	500 units/g, ointment	Up to three times a day	Complex with zinc results in stability Commonly combined with polymyxin/neomycin Delayed allergic reactions reported Good alternative to silver sulfadiazine in patients with burn who are allergic to sulpha drugs
Retapamulin	Impetigo, secondarily infected dermatitis or traumatic lesions	1% ointment	Twice daily for 5 days	Low systemic exposure and favourable tolerability profile
Fusidic acid	Mild to moderately severe SSTI (impetigo, folliculitis, erythrasma, furunculosis, etc.), eczema	2% cream/ ointment	3-4 times daily for 1-2 weeks	High penetration ability Side effects are unusual, but few patients report skin irritation
Metronidazole	Rosacea	0.75% and 1% gel/cream	Twice daily for 6-12 weeks	Improves inflammatory lesions (papules and pustules) and erythema but has no effect on telangiectasia
Clindamycin	Acne vulgaris	1% solution (contains alcohol) 1% gel	Twice daily for 6-12 weeks	Increases drug-resistant resident skin flora (risk of Gram-negative folliculitis)
Erythromycin	Acne vulgaris	2% solution (contains alcohol)	Twice daily for 6-12 weeks	Gradual decrease in the efficacy due to emergence of drug-resistant *Propionibacterium*
Tetracycline	Acne vulgaris	3% solution/ cream	Twice daily for 8 weeks	n-decyl methyl sulfoxide enhances its penetration Side effect may include slight yellowish discolouration of skin and transient stinging or tingling sensation Infrequently prescribed topically
Mafenide acetate	Burn wound	8.5% cream 5% aqueous solution	5% solution must be applied to saturate gauze dressings	Synthetic drug closely related to sulfonamines - avoided in patients with allergy to sulpha drugs, G-6-PD deficiency Excellent tissue penetration, including eschar Prolonged use can result in overgrowth of *Candida* species Used with caution in patients with large burns or renal dysfunction

Contd...

Table 1: Contd...

Drug	Skin infection	Formulation	Dosage	Comments
Chloramphenicol	Acute otitis externa	5%, 10% drops	2-3 drops 2-3 times daily	Reports of delayed-type hypersensitivity
Polymyxin B+bacitracin	Acute otitis externa	Ointment (7500 IE/g polymixin and 300 IE bacitracin)	Twice daily for 2 weeks	The addition of hydrocortisone acetate with antibiotic improves symptoms better than steroid-free ointment
Ciprofloxacin, ofloxacin	Chronic suppurative otitis media, acute otitis media in children with grommets	0.3% solution	3 drops, 2-3 times a day for 14 days	Treatment of choice for acute otitis media with tympanostomy tubes
Drug	**Eye Infection**	**Formulation**	**Dosage**	**Comments**
Azithromycin	Blepharitis Keratitis Conjunctivitis	1.5% single-use drops	One drop twice daily for 3 days	Poor corneal penetration
Chloramphenicol	Conjunctivitis	0.5% drops (single and multi-dose) 1% ointment	2 drops every 3 h	Good corneal penetration
Ciprofloxacin	Conjunctivitis Corneal ulcer	0.3% drops/ ointment	Drop: 1-2 drops four times a day (2-hourly for the first 2 days if severe); continue for up to 21 days Ointment: 1.25 cm three times daily for 2 days, then twice daily for 5 days or longer	Good corneal penetration Not recommended in patients>2 years of age
Fusidic acid	Conjunctivitis	1% drops	1 drop twice daily	Good corneal penetration
Gentamicin	Conjunctivitis Blepharitis	0.3% drops	1 or 2 drops up to six times daily (every 15-20 min in severe infection)	Excellent corneal penetration, side effect: Macular infarct at doses even >0.1 mg
Levofloxacin	Conjunctivitis	0.5% drops (single and multi-dose)	2-hourly up to eight times daily for the first 2 days and then four times daily for 3 days	Good corneal penetration, not recommended below 1 year of age
Moxifloxacin	Conjunctivitis Endophthalmitis	0.5% drops Intravitreal 400 µg/0.1 ml	1 drop three times daily usually for 7-8 days	Good corneal penetration
Ofloxacin	Conjunctivitis	0.3% drops	Every 2-4 h for 2 days and then four times daily for 10 days	Good corneal penetration, not recommended below 1 year of age
Tobramycin	Conjunctivitis	0.3% drops	Twice daily for 6-8 days (four times if severe infection) then daily for 5-7 days	Excellent corneal penetration, not recommended below 1 year of age

SSTI: Skin- and soft-tissue infection, *S. aureus: Staphylococcus aureus*, MRSA: Methicillin-resistant *S. aureus*, *P. fluorescens*: *Pseudomonas fluorescens*

relatively ineffective. In burn wounds, a race for dominance exists between the human keratinocytes and microbes. In addition to surgical excision, grafting, critical care and nutrition, topical antimicrobials are an important component in the armamentarium of burn and wound care. Topical agents are also used to treat uncomplicated primary skin infections such as acne, impetigo, dermatitis and folliculitis. By suppressing microbial growth, they tilt the balance in favour of the skin cells, aiding in healing. There are two superclasses of topical antimicrobials: antiseptics and antibiotics. Antiseptics include emulsifiers, acids, heavy metals and oxidisers. Antibiotics include agents such as aminoglycosides, bacitracin, mafenide acetate, mupirocin, nitrofurazone and various other agents [Table 1]. Firmocidin, isolated from normal skin commensal (*Staphylococcus epidermidis*), is a broad-spectrum antibiotic with low toxicity for human cells and is used for the treatment of skin infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and Streptococci.[2] Second, retapamulin is approved by the Food and Drug Administration (FDA) for the treatment of impetigo, with *in-vitro* activity against MRSA and drug-resistant Streptococci with a low propensity to cause mutational resistance.[3] Topical neomycin

and framycetin (both derived from *Streptomyces* spp.) have been found to be effective in treating primary and secondary skin infections caused by Gram-negative organism[4] and lastly, usnic acid, a lichen-derived secondary metabolite with a dibenzofuran structure, has antimicrobial activity against Gram-positive, biofilm-producing bacteria and MRSA. A new class of topical agents, nucleotide derivative compounds with broad-spectrum antimicrobial activity i.e., 'Nubiotics', have shown promising results in treating burn wound infections caused by *Pseudomonas aeruginosa*.[5]

For the treatment of acne, tetracyclines have been commonly used systemically. However, as they are chemically unstable with a tendency to degrade by oxidation, they are rather unsuitable for topical application.[2] Other agents, erythromycin and clindamycin, inhibit both protein and lipase synthesis, making them ideal for such infections as lipase is essential for the hydrolysis of serum triglycerides to glycerol, a substrate utilised by *Propionibacterium acnes*, a common agent causing acne.[6] The desquamating effect of retinoids and benzoyl peroxide increases antibiotic penetration, providing rationale for use in combination.[7]

Eye infections

Bacterial conjunctivitis, chronic blepharitis and keratitis are common ocular infections where topical antibiotics are frequently used. The commonly used topical antibiotics and their clinical applications are presented in Table 1.

Apart from primary eye infections, the use of topical antibiotics during the preoperative period is also practiced in various centres, to reduce the incidence of post-operative infection. Although some studies show a decrease in positive conjunctival cultures in such cases, a recent meta-analysis did not find any evidence favouring the use of post-operative antibiotics.[8,9] With such conflicting evidence, it seems only reasonable that the use of topical therapy should be based on clinical evidence and experience of the concerned practitioner in these cases.

Ear infections

Topical antibiotics have been found to be as effective as oral antibiotics for the management of ear infections. In patients with chronic suppurative otitis media, topical and combination (intravenous and topical) ciprofloxacin were found to be equally effective.[10] In a systematic review by Rosenfeld *et al*., evaluating the use of topical antimicrobials for otitis externa, clinical cure rates of 65%–80% were observed within 10 days of treatment, showing a high efficacy.[11] However, evidence from randomised controlled trials in children with grommets (a middle ear ventilation tube) and ear discharge convincingly demonstrate superior activity to oral administration.[12,13]

Selective digestive decontamination

Selective digestive decontamination (SDD) is a prophylactic strategy aimed at preventing or reducing endogenous infections in critically ill patients. It has been evaluated in burn patients;[14] critically ill children[15] and patients undergoing oesophageal, gastric, or colorectal surgeries.[16] The full regimen of SDD includes a short course of systemic antibiotics followed by the use of enteral agents such as a combination of polymyxin-E, tobramycin and amphotericin-B, administered into the gut orally or through the nasogastric tube.[17] Aminoglycosides, such as neomycin and paromomycin, have been shown to be effective in acute episodes of hepatic encephalopathy (HE). However, despite the poor intestinal absorption, both ototoxicity and nephrotoxicity have been reported following the use of these agents.

Rifaximin, a non-aminoglycoside, semi-synthetic, non-systemic, highly bile-soluble drug, offers good activity in the small intestine and limited activity in the aqueous environment of the colon. It has low systemic absorption and has shown to have benefit in acute HE, preventing HE recurrence[18] and in reducing the incidence of infections in severely ill liver transplant recipients.[19,20] However, a higher association of rifaximin treatment with the development of *Clostridium difficile* colitis has been reported in some studies,[18] leading to a long-standing debate among experts regarding whether SDD should be used or not. Nonetheless, rifaximin is indicated for refractory HE not responding to standard therapy, treatment of travellers' diarrhoea by non-invasive strains of *Escherichia coli* and even in irritable bowel syndrome with predominant diarrhoea.[21]

Dental infections

The development of early childhood caries in high-risk children is lowered by using topical antibacterial agents, such as chlorhexidine and povidone-iodine.[22,23] Slow-release gels of doxycycline and thin strips with tetracycline placed between the infected gum and tooth, minocycline and even metronidazole are used commonly for the management of gum infections.[24] Unlike oral antibiotics, topical treatments deliver relief directly to the affected gum tissue. In patients undergoing dental procedures, topical amoxicillin decreases the post-procedural incidence of bacteraemia and is used for endocarditis prophylaxis.[25]

Lower respiratory tract infections

The rationale for inhaling antimicrobials is to maximise the drug delivery to the target site and limit the potential for systemic adverse effects. Early formulations were poorly tolerated by patients due to side effects such as bronchospasm and bronchial irritation, which have been overcome by preservative-free preparations, with osmolarity matching airway surface liquid.[26] At present, cystic fibrosis (CF) is the only pulmonary condition where the FDA has approved the use of inhaled tobramycin in patients with chronic *P. aeruginosa* infection.[27] Reduction in bacterial load lowers the risk of exacerbations, improves symptoms and decreases unscheduled hospitalisations. A recent systematic review assessed the performance of inhaled antibiotics in non-CF bronchiectasis, and inhaled aminoglycosides were reported to have acceptable safety profile.[28]

Inhaled antibiotics have also been recommended in the treatment of hospital-acquired and ventilator-associated pneumonia due

to bacteria only susceptible to aminoglycosides or polymyxin and in case of patients not improving on intravenous therapy.[29] The key advantage of using aerosolised antibiotics is that the levels achieved in the lungs are logs greater than what can be achieved by intravenous dosing. By adding inhaled antibiotics as an initial empirical therapy, substantial bacterial killing can be seen even if typical intravenous antibiotic therapy is ineffective.[30] However, inhaled drug delivery is challenging in mechanically ventilated patients. In addition, drug lost into the environment during nebulisation may cause inadvertent antibiotic exposure in healthcare workers. A summary of the various inhaled antibiotics available and a description of their therapeutic potential is shown in Table 2.

Vulvo-vaginal infections

Topical and oral preparations of metronidazole and clindamycin are used for the management of bacterial vaginosis (BV). Topical preparations have fewer gastrointestinal (GI) side effects, better compliance and less association with subsequent *Candida* infection.[31]

Factors Affecting Efficacy of Topical Agents

In case of topical drugs, generically equivalent preparations may not be therapeutically equivalent. Apart from the components of the formulation, other factors influencing the absorption and efficacy include pH, ionic nature, viscosity, spreadability and the proportions of oil/water/surfactants/preservatives/stabilisers. Exposure to heat or light and prolonged storage duration can also influence the relative stability of topical formulations due to oxidation or degradation. In this section, we discuss the various factors which influence the efficacy of topical antimicrobial agents [Figure 1].

Drug formulation

The formulation of topical therapies is as important as the antibiotics itself because interaction of the vehicle with surface (skin/mucosa) can alter drug efficacy. The formulation must ensure that the antibiotic is delivered to target site, maintaining the dosage integrity and duration of activity. Some additives, for example zinc oxide used in dusting powders, borax and chlorocresol used in creams, may themselves exhibit antibacterial properties. The distribution of antibiotic also depends on the vehicle used and the molecular weight of the drug, and percutaneous absorption is inversely proportional to the latter. In addition, the lipid/water partition coefficient for optimal skin permeability should be more than or equal to 1. The various topical formulations available for topical antibiotics include:

- Solid topical formulation: Antibiotic powders containing chemically inert compounds such as kaolin, talc, zinc

Table 2: A summary of the clinical use of inhaled antimicrobials

Inhaled antimicrobial	Indication	Formulation	Dose/duration	Key outcome	Side effects	Additional comments
Tobramycin	CF patients aged ≥6 years with *P. aeruginosa*	TSI TIP	80 mg - TID/32 months or 600 mg - TID/12 weeks or 300 mg - BID 28 days 112 mg - BID/28 days	Improvement in pulmonary function Improved symptoms Decrease in bacterial density Decreased hospitalisation rates Efficacy of TSI and TIP is comparable	Cough, voice alteration, tinnitus	Tolerability of TIP is lower than the TSI
Aztreonam	CF patients aged ≥6 years with *P. aeruginosa*	AZLI	75 mg - BID or TID/28 days	Decreased exacerbation rates Improved pulmonary function Reduction in hospitalisations	Cough, headache, bronchospasm, nasal congestion and rhinorrhoea	IV aztreonam has arginine associated with declining lung function in patients with CF when inhaled Consider giving a monitored trail dose first, especially in patients with severe lung disease
Colistin	Approved by EMA for the management of chronic infections due to *P. aeruginosa* in CF patients aged ≥6 but not approved by US FDA	CSI CDP	1 million units - BID/3 months or 80 mg - BID/4 weeks or 1.6 million units - BID/28 days	Slower decline of pulmonary function Decrease in bacterial load	Bronchospasm	Mixing colistin with sterile water converts to the bioactive form comprising of polymyxin E1 which is toxic to lung. Thus, avoid premixing and storing >24 h must be avoided
Fluoroquinolones	Not approved	LSI CiDP	120 or 240 mg - BID/28 days 32.5 mg or 48.75 mg - BID/28 days	Slight improvement in lung function	Cough, taste disturbances, tiredness or weakness	Contraindicated in pregnant or breastfeeding, epilepsy and history of tendon disorders

CF: Cystic fibrosis, TSI: Tobramycin solution for inhalation, TIP: Tobramycin inhalation powder, *P. aeruginosa: Pseudomonas aeruginosa*, IV: Intravenous, CSI: Colistin solution for inhalation, TID: Thrice a day, EMA: European Medicines Agency, CDP: Colistin dry powder, LSI: Levofloxacin solution for inhalation, CiDP: Ciprofloxacin dry powder, FDA: United States Food and Drug Administration, BID: Twice a day, AZLI: Aztreonam solution for inhalation

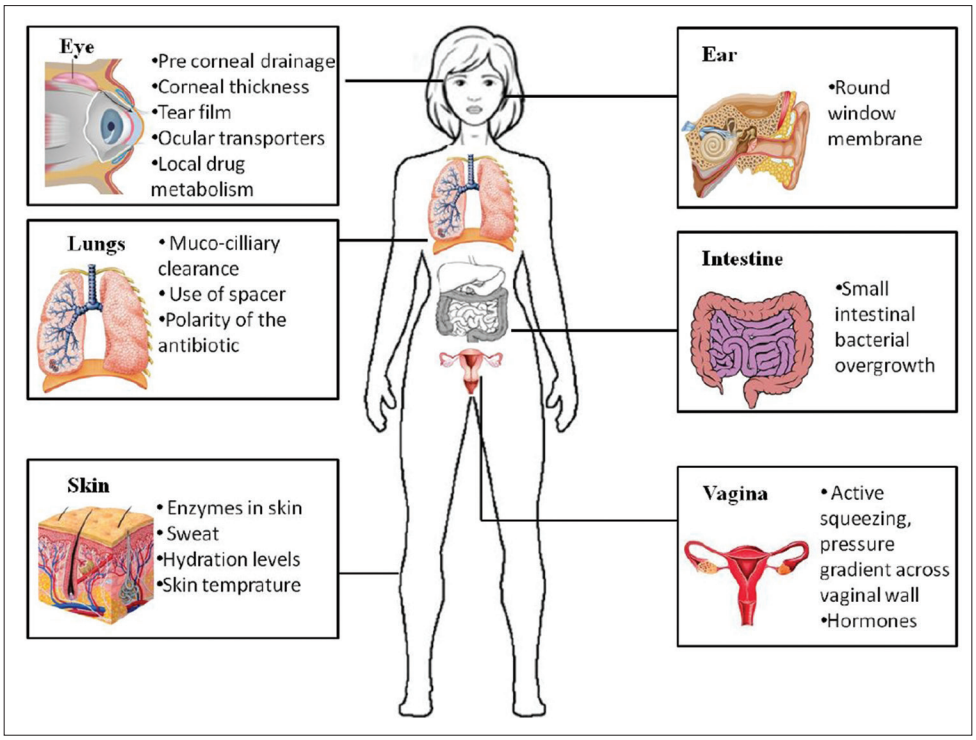

Figure 1: Factors affecting the efficiency of topical antibiotics at various sites of the human body

oxide or starch are available for application on wounds for absorbing moisture to retard bacterial growth and allay local irritation. Clarithromycin dusting powder and neosporin (neomycin, polymyxin B and bacitracin combination) have been widely used for burns and minor skin infections. Dry powder inhalation for the delivery of local antimicrobial to the lungs is also available

- Semi-solid topical formulation: This includes creams, ointment, gels and pastes. Creams are semi-solid emulsions which are less occlusive or greasy, have easier spreadability, are easier to wash compared to ointments and are best for moist lesions. In case of ophthalmic delivery, ointments have an advantage of longer retention in the cul-de-sac, resulting in longer drug action. They also prevent drying of the ocular surface and minimise lid stickiness in patients with conjunctivitis. However, as the antibiotic leaves the vehicle less rapidly in ointments, a slower onset of action and lower peak concentration are expected. Gels are transparent or translucent semi-solid topical formulations used for the treatment of acne, periodontal disease and BVs. Pastes are thick preparations with a high amount of starch, zinc oxide, calcium carbonate or talc and are less greasy than ointment but have a long retention time unlike creams and gels
- Liquid topical formulation: This includes low-to-medium viscosity preparations for application on unbroken skin. Eye drops are also liquid formulations which provide faster action with higher peak concentrations but at the cost of shorter half-life.

New vesicular formulations such as liposomes, micro-emulsions and nanoparticles have been shown to potentiate cutaneous drug delivery.[32] Topical ocular antibiotic microsuspensions and nanosuspensions increase the ocular residency time, peak drug levels and duration of action.[33,34] Incorporation of antibiotics into dressings and using alginates, sponges and foams allow for controlled local release. Bioadhesive and thermogelling approaches have been proposed to improve the delivery of traditional drugs.

Drug dosing and duration of contact

Determining the effective dosing volume and dosing interval and assessing local safety in changing the dosing regimen of topical drugs are difficult. The extent of application of topical medication varies between different patients depending on their personal preference. For application on skin, generally, a 1.6-mm-thick layer is recommended, twice or thrice a day. However, some patients may use a drug sparingly or in excess based on their own judgement, and there is no way to measure the amount of drug actually present on the site. Other factors such as sweating, physical activity and inadvertent removal of drug by children may also have bearing on the drug efficacy.

The contact time needed for the action of most topical preparations is not known, and the duration of treatment is also controversial. While some patients may stop drug application on symptomatic improvement, others may continue long-term treatment despite no response, and these interpersonal variations could account for variable response.

Pseudo-eschar formation

Another element of concern while treating with topical agents is the reaction of drug with other physiological components. Pseudo-eschar is an adherent layer of exudates formed due to the interaction of inflammatory exudates and protein coagulum with the use of topical antibiotic creams over wounds, especially deep burns. Preparations containing collagenases are associated with less pseudo-eschar formation and may be preferred while treating such cases.[35]

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth has been seen to be associated with the induction of cytochrome (CYP) 3A4 enzyme in patients treated with rifaximin, commonly used for intestinal decontamination. Conditions where the intestinal permeability is increased due to mucositis, portal hypertension secondary to cirrhosis, etc., may also be associated with variable levels of locally acting agents in the intestine.

Pharmacokinetics of Topical Agents

By definition, PKs is the study of the relationship of dose and time of any administered drugs with the assumption of fictional body spaces such as the intravascular compartment and extracellular and intracellular spaces. One of the major challenges in the PK studies of topical agents is the ambiguity in the measurement of drug levels following topical delivery.

Ocular pharmacokinetics

The estimation of PK parameters in ocular tissues is challenging due to the complex anatomy of the eye and the presence of dynamic physiological barriers. The factors that may affect the PKs of ocular drugs are:

- Precorneal: After instillation of drug, approximately 80% is drained into the naso-lacrimal duct, and systemic drug loss lowers the ocular bioavailability.[36] The rate of drainage depends on the instilled volume, which is directly proportional to the rate of drainage especially for liquid formulations. This 'washout effect' is enhanced due to the tear fluid turnover and blinking and decreased in preparation with higher viscosity decrease. As some antibiotics may be active as acidic or alkaline solutions, excessive tear secretion and drug loss may be seen in some preparations. Thus, the pH of ophthalmic preparations is usually adjusted to 7–7.7. Increased tonicity may also increase tear formation, and a tonicity equivalent to 0.5%–1.8% sodium chloride is preferred.[37] Nearly 0.7% of the total body protein is present in the tear film, and proteins such as lipocalin can bind to antibiotics, thereby resulting in a reduction in the total available free drug. Binding to pigmentary structures such as melanin also affects the PK, and differences in the PK for brown- versus blue-eyed individuals have been reported[36]
- Corneal: Corneal permeability is not comparable for all topically applied drugs and is perhaps the most effective barrier to drug penetration. The lipophilic cellular monolayer of corneal epithelium is more susceptible to penetration by lipophilic antibiotics (e.g., fluoroquinolones, macrolides, tigecycline and lincosamides). Hydrophilic antibiotics (such as beta-lactams, aminoglycosides, tetracycline and polymyxin) permeate through the conjunctiva and sclera to the anterior chamber (AC) and ciliary body. Mucin forms a gel-like structural barrier over the cornea and conjunctiva; however, there is no direct evidence indicating its role in affecting ocular bioavailability[38]
- Enzymes and transporters: Various enzymes such as CYP P450, cyclooxygenase, aldehyde/monoamine oxidase, aldo/ketone reductase, hydrolase and transferase are expressed in ocular tissues. They are mainly released from the cornea, lens, ciliary body and even the retina. In addition, several xenobiotic transporters in the cornea, AC and retina also play an important role in ocular PK.

Dermatokinetics

The skin is a heterogeneous multilayer tissue forming an effective barrier against the absorption of exogenous compounds. The outermost layer, the stratum corneum, is composed of corneocytes arranged in a dense configuration with intercellular lipids. When hydrated, the corneocytes swell, and their thickness increases nearly threefold, resulting in reduced diffusion path length and protein network density, favouring the drug transport. Damage to the epidermis as seen in wounds, burns etc., also increases the permeation across skin. In addition, the dermis contains various drug-metabolising enzymes including CYPs, transferases, hydrolases and sulfatases, which alter the structure and charge of drugs influencing permeability.[39] Formulations with moderate pH values, typically higher than the isoelectric point of skin (pI~4), are appropriate for topical delivery.

Pharmacokinetics of inhaled antibiotics

Following the inhalation of any drug, only a small fraction (10%–60%) is deposited in the airway and the rest is swallowed and absorbed into systemic circulation if orally bio-available. Thus, blood concentration of inhaled drugs is determined by the amount of drug absorbed from both the lungs and GI tract, and blood-based PK studies are not a true representation of their pulmonary fate. There is limited data on dose delivered to airway, pulmonary available dose and residence time of inhaled antibiotics. For drugs that are slowly dissolving, mucociliary clearance determines the difference in the amount of drug in the lung versus bloodstream. In case of administration via large-volume spacers, the amount of drug swallowed is reduced, but other factors influencing drug absorption include the number of actuated puffs and the time delay between inhalation and actuation.[40] Pulmonary bioavailability is also affected by antibiotic polarity and as aminoglycosides are hydrophobic, the absorption from gastrointestinal tract is poor, making blood levels a good reflection of absorption across the alveolar vascular bed compared to bronchial mucosa.[40]

Pharmacokinetics of intravaginal antibiotics

The distribution of any drug through the vaginal environment

is a mass transport process involving several active forces (such as squeezing by the vaginal wall, pressure gradient imposed on the vaginal canal and surface tension) in addition to passive drug diffusion. There are very few studies evaluating the PKs of vaginal drug delivery, and there is limited knowledge regarding the quantity (approximately 1–2 ml) and distribution of ambient fluid in the vagina. The vaginal environment is also influenced by hormonal changes during the menstrual cycle and by age, subsequently affecting the transvaginal drug distribution, making it highly non-uniform.

Antimicrobial Susceptibility Testing for Topical Agents

The prime attribute of the breakpoint minimum inhibitory concentration (MIC) is its correlation to the achievable drug levels when standard dosing is used. However, practically, the serum concentrations may be lower for drugs that are being directly applied to the target site. Hence, the MIC breakpoints provided in guidelines which consider serum drug levels derived from systemic dosing regimens cannot be applied to topically applied agents. Although *in-vitro* AMST using standard protocols is an important component in the management of infectious diseases, the MIC values must be interpreted in the light of the expected concentration of drug at the site of infection. The traditional methods used to assess the kinetics of drug in blood or urine may not be applicable to most topically applied molecules as they do not produce measurable levels in extracutaneous body fluids. Unfortunately, there is a lack of specific, standardised tests for the evaluation of the efficacy of topical agents. In case of topically applied skin preparation, for example, it would be more promising to study the drug absorption and elimination from the SC. This is done in the dermato-PK approach, in which the levels of drug are continuously or intermittently determined over a period of time.

New methods for AST testing for topical agents

Agar well diffusion

In this method, agar plates with punched-out wells are used and lawn culture of the bacterial isolate is performed.[41] The wells are filled with the topical agent in its commercial form. For semi-solid formulations, the drug is diluted and a range of dilutions are used, and the plates are incubated at 37°C for 24 h. A zone of inhibition defined as a clear region around the well containing the antibiotic is measured, and larger zones indicate higher potency of the preparation.[42] An analysis of about ten strains can be performed over an hour of bench manipulation, including dilution of the commercial topical preparation. However, agar well diffusion is not standardised and reference strains are not available for AST of topical antimicrobials. Thus, assays with comparison of the results with the whole reference population are needed for the validation of this technique following which it can be used in semi-routine practice of AST.

Cell-associated cell protection assay

In addition to the actual antibacterial activity of any topical preparation, the efficacy of topical antibiotics also depends on their ability to associate with epithelial cells. This contribution is not typically measured by the standard AST methods which only consider the antibacterial activity. A novel assay, the cell-associated cell protection assay (CACP), has been described which measures the ability of test antibiotics to associate with mammalian epithelial cells and protect them from bacteria. The epithelial cell layer integrity is studied by gentian violet staining, and the minimum cell layer protective concentration of the antibiotic is determined. This method has been used for azithromycin, erythromycin, tetracycline and bacitracin AST in ocular isolates of *Staphylococcus aureus* by Wingard *et al*.[43] They reported that bacterial susceptibility to bacitracin which was present on testing with traditional AST methods, failed to show consistent protection of human cells using CACP, highlighting the role of such *in-vitro* assays while determining therapeutic dosing regimens.

Current guidelines on AST of topical agents

Antimicrobial susceptibility guidelines are very important in the management of any infections as they play a crucial role in summarising the current evidence base, standardising antibiotic choice and subsequently improving clinical outcomes. However, there are many reasons why the currently available recommendation of AST cannot be applied to topical preparations and breakpoints for topical agents have been repeatedly requested from agencies reporting AST guidelines.

In 2012, the European Committee on AMST proposed that epidemiological cut-off values (ECOFFs) should be used for indicating the susceptibility to topical agents by categorising isolates as wild type or no-wild type.[44,45] These guidelines have been suggested only for skin, ocular and ear infections and not of GI and inhaled antibiotics. Although specific breakpoints for nasal decontamination of *S. aureus* by mupirocin are available, the ECOFFs for many organisms and topical agents are yet to be defined.

One practical concern regarding the reporting of ECOFF-based breakpoints for topical agents is that, as the systemic breakpoints may be only slightly different from the topical breakpoints in some cases, it may be confusing to report ECOFF-based cut-offs for agents used both topically and systemically. In addition, there is absence of data relating MIC of infecting organisms to clinical outcome, making it difficult to reach a consensus regarding the use of these ECOFF-based cut-offs.

Thus, the proposal was revised, and it was suggested that the topical and systemic breakpoints should be the same for drugs which are also used systemically. Moreover, ECOFF-based breakpoints should be used only in those drugs for which only topical preparation is available.

Limitations of Using Topical Antimicrobials

Although topical formulations have numerous advantages, one of the chief concerns is the difficulty in monitoring antibiotic

dosage and duration of therapy. Although generally assumed to concentrate at the site of application, the actual drug levels are difficult to measure. As most topical preparations are applied on sites with pre-existing normal bacterial flora (such as skin, eye and gut), the detrimental effect of antibiotic on the 'good' bacteria is difficult to control.[46] As a drug cannot differentiate between the colonised and the pathogen, unnecessary exposure of the resident microflora to high drug levels may select drug-resistant phenotypes.[47] This emergence of resistance has been seen in *Staphylococcus* due to the indiscriminate use of topical mupirocin and fusidic acid.

Conclusion

The number of antibiotics available and the quality and composition of the formulations recommended for topical drug delivery are improving. Their role in the prevention and treatment of locally invasive infections is established for many clinical conditions. However, there is still a lacuna in the translation of the PK knowledge of these topical preparations to clinical practice. In view of the various factors which influence the activity of these agents, it is imperative to conduct systematic studies for assessing their utility in diverse clinical scenarios. In addition, reporting the clinical outcome following the use of these agents and its analysis in the light of the recently proposed ECOFF-based cut-offs is also an area which merits further research.

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Conflicts of interest

There are no conflicts of interest.

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