

Review Article

Topical Antibacterials and Global Challenges on Resistance Development

Sathish Amirthalingam^{1*}, Kok Shin Yi², Lim Tze Ching² and Ng Yoke Mun²

¹Department of Pharmacy Practice, ²Department of Pharmacy, International Medical University, No. 126 Jalan Jalil Perkasa, 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

*For correspondence: **Email:** asathish1981@gmail.com, SathishAmirthalingam@imu.edu.my; **Tel:** +60 11 16185873

Received: 10 October 2014

Revised accepted: 10 April 2015

Abstract

Purpose: The skin acts as the first line of defence against the invasion of microorganisms. Damage to the skin such as abrasion, bruises and trauma will expose underlying tissue to bacterial infection. Minor skin infections can be easily treated with topical antibacterial medication that is available over the counter or by prescription. On the other hand, serious bacterial skin infections can be life-threatening and may require complex interventions such as medical or surgical methods to cure the disease. The treatments given have to be assessed according to the presentation, aetiology, chronicity of the wound (depth and size) and/or skin lesions. For skin bacterial infection, topical route of administration is preferred over systemic administration due to the delivery of a higher concentration of medication for the former into the desired area. It is also less likely to cause systemic side effects, toxicity, and bacterial resistance. There is ongoing controversy and debate regarding the likelihood of developing bacterial resistance with the usage of topical antibiotics as an antibacterial. This could be due to inappropriate antibiotic use resulting from self-medication, over the counter availability, prescribing on demand and a lack of regulatory control.

Keywords: Topical antibacterial, Bacterial resistance, Self-medication, Inappropriate antibiotic use, Dispensing

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INTRODUCTION

The skin undoubtedly is the first line of defence against a broad range of bacterial. When the skin integrity is breached accidentally or purposely, its natural defences will thus be weakened and topical medication may be prescribed [1]. A topical medication refers to medication that is applied to body or tissue surfaces such as skin and conjunctiva [2]. Topical antibacterial drugs are commonly dispensed items by community pharmacists specifically for topical bacterial infection. Its role is to either kill or inhibit the growth of microorganism and can be used for both prophylaxis as well as treatment of

superficial infection [3,4]. Topical antibacterial drugs are currently available in many forms such as gels, creams, ointments, sprays and liquids [2-4]. They either contain a single antibiotic ingredient or are in combination with other antibiotics or corticosteroids. Community pharmacy have a variety of topical antibacterial agents which are available for potential use in; acne vulgaris, pyoderma including impetigo, folliculitis, rosacea, infected eczema, secondarily infected traumatic skin lesions, prevention of infection in minor cut or burn, eyes and ear infection [5].

Nowadays, most people seek advices in managing their minor ailments from community pharmacists rather than seeking consultation from general practitioners (GP) [5]. This is supported by the data revealing that more people with skin infections (21.5 vs 20.5 %) and acne (6.6 vs 2.9 %) had purchased over-the-counter (OTC) products from pharmacy rather than visiting general practitioners. A survey also revealed that the public usually sought advice from community pharmacists for diseases include topical bacterial infection such as acne, eczema/dermatitis and impetigo [5-7]. In short, as the multidrug resistance incidence spreads globally and pose threat to our society, extensive international initiatives will be essential to curb its consequences. Meanwhile, the responsible use of topical antibiotic should be practiced especially among the primary healthcare settings where their main role is to make sure that the health services are accessible by the public.

Nature of bacterial infections and topical antibacterials

The advantages of topical route application as compared to systemic administration include the decreased risk of systemic side effects and even toxicity, reduced the possibility to elicit bacterial resistance, and the application of high concentration of antibacterial agent at the site of infection which will increase the effectiveness of the treatment [1]. Generally, skin infections are caused by many different types of bacteria. Most infections are due to gram-positive microbes such as *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus viridans* and so on. However, gram-negative bacteria infections can also occur. Examples of common gram-negative bacteria are: *Escherichia coli*, *Haemophilus influenza*, *Clostridium* species, *Mycobacterium* species, *Pseudomonas* species, and other anaerobes [1]. The use of antibiotics is very crucial, for instance; use the topical antibacterial agent only when a clear medical indication has been confirmed and as long as necessary to achieve the desired effect, use preferably combination therapy that minimizes the risk of bacteria resistance, and better use alternatives other than antibiotics when possible [8].

Condition and availability of topical antibacterial

Nowadays, the production of countless topical over-the-counter topical antibiotic products have provided benefits to public health by reducing bacterial load on skin. The term topical

antibacterial usually refers to both antimicrobial and antiseptic agents [9]. While the use of topical antibacterial is very common however, emergence of antibacterial resistance incidences had raised the concern worldwide. A steady supply of new antibiotics in the past that is effective against continuously emerging resistant strains adequately addressed resistance concerns [10]. However, nowadays, the combinations of different types of antibacterial not only enable bacteria to develop single resistance, but also multiple resistances. In alarming contrast to the past, today's antibacterial research and development pipelines are nearly dry due to the rising resistance in conjunction with a lack of antibacterial innovation [10].

Topical antibacterial drugs are one of over-the-counter (OTC) medications which is also known as self-medication products [11]. Common topical antibiotics that can be found in OTC are bacitracin, neomycin, fusidic acid, clindamycin, mupirocin, gentamicin, erythromycin, polymyxin B and chloramphenicol [12,13]. These topical antibiotics are available as sole agent as well as in combination with other topical antibiotics or with topical corticosteroids [12,14].

Nowadays, community pharmacists are seen as first-line healthcare professionals for consultations [15,16]. Several studies stated that role of community pharmacists in the management of dermatological problems has increased dramatically over the decades [13,14]. Thus, the knowledge of community pharmacists in skin diseases is very vital [13,17]. Since topical antibacterial drugs are OTC medications, community pharmacists inevitably play a crucial role in dispensing, advising and counselling of these OTC products [18].

Global challenges

Usage of topical antibacterial drugs

There is lack of study on the perception and experiences of community pharmacists on the usage of topical antibacterial in community pharmacy settings. However, there are several surveys conducted worldwide on the use of combination topical antibacterial drugs by various healthcare sectors. For instance, National Ambulatory Medical Care Survey (NAMCS) in United States reported that combination of topical antibiotics products such as polymyxin/bacitracin, and neomycin/ polymyxin/ bacitracin are commonly used by all physicians

whereby they appeared to be the top 20 list of over-the-counter products used [11].

Besides, Tucker's study stated that community pharmacists felt comfortable in dispensing topical antibiotics. They wished to have topical antibiotic-steroid combination and topical antibiotics available as non-prescription/over-the-counter products. Moreover, topical antibiotic-steroid combination was also widely used in United Kingdom because evidence has shown that such combination products are more effective in the management of infected eczema. Nonetheless, it is also believed that popular usage of topical antibiotic-steroid combination products also influences pharmacists' belief that this combination was generally more effective in treating skin diseases [14]. Another observational study by Davis *et al*, found that the sales of topical chloramphenicol increased to 47.8 % from year 2005 to 2007 after this topical antibiotic was made available over-the-counter [19].

Dispensing of topical antibacterial drugs in community pharmacy

Topical antibacterial drug is one of the over-the-counter medications in which patient can obtain conveniently from community or retail pharmacies without a doctor's prescription [11, 18]. This means that patients can use topical antibacterial drugs for self-medication in treating topical infections [18]. Community pharmacists as the primary source for OTC medications counselling should obtain patients' information which is critical to the case presented, then provide all necessary information and advice on medication, as well as assisting patient in choosing an appropriate treatment regimen to promote safe and effective use of medication [16,18,20]. Nonetheless, Wabe's research reported that community pharmacists often failed in obtaining vital clinical information from the patients and there was little knowledge on drug usage [20]. This is supported by another study carried out in Portugal, whereby it mentioned that

community pharmacists normally counselled patients on the standard dosage of antibiotic as they did not know the severity of infections though correct dosage depends upon the severity [15].

On the other hand, two studies have proposed that when community pharmacist deal with dermatological problems, they would refer to published journal articles, followed by reference books, while media (television or radio) and wholesaler are less likely to influence pharmacists in the treatment of skin problems [17,20]. Besides, Wabe's study stated that most of the community pharmacists would refer to patient's information leaflets and books, but this was not recommended as it contained manipulated information which may cause bias [20]. The guidelines for selection of appropriate topical antibacterial is provided in Table 1.

Factors affecting dispensing OTC products by community pharmacists

To date, there are not many studies on the factors influencing the dispensing of topical antibacterial drugs by community pharmacists. However, as mentioned previously, topical antibacterial drug is one of the common over the counter (OTC) products, several studies did reflect on the factors affecting the selection of OTC products by community pharmacists. For instance, a study carried out in Northern Ireland revealed that medications safety was the main considerations in selecting an OTC product. However, patient product and professional factors were also involved in the decision making [33]. Apart from this, a study in Northeast Ohio showed that the main sources of information that usually influence community pharmacists selection of OTC products for dermatology conditions was pharmacy journals, followed by internet based sources and pharmacy settings with 62, 24 and 8 %, respectively [21].

Table 1: Guidelines for selection of appropriate topical antibacterial [39]

Skin type	Treatment vehicle	Comment
Sensitive/dry skin	Cream	Non-irritating, non-drying
Oily skin	Gel	Drying effect: certain kinds of cosmetics may not adhere to gel: may cause burning irritation
	Solutions	Mainly used with topical antibiotics
Any type	Lotion	Spread well over hairy areas: contains propylene glycol, which has burning/drying effects

Topical antibacterial drug resistance

There are evidences showing the increase rates of antibacterial resistances from the use of topical antibiotic formulations. For instance, a study in United Kingdom (UK) showed that the number of patients carrying strains of *Propioni bacterium* resistant to clindamycin, erythromycin as well as tetracycline increased almost two folds within six years (1991 – 1997) and the resistance rates are as high as 55.5 % in year 2000. Among the three topical antibiotics mentioned, resistance to erythromycin was more common and it was found to be cross-resistant with clindamycin. Resistant to tetracycline on the other hand only increased a little over the time [22]. Besides that, fusidic acid also showed an increased resistance rates from 4.6 to 12.4 % from year 1994 to year 1997 in Western Australia while in New Zealand, the resistance rates increased from 2.4 to 17 % from year 1982 to year 1999 [23,24]. Moreover, mupirocin which is commonly used in acne treatment also showed to be having increased resistance rates especially to the *S. aureus* strains [25].

All these studies demonstrate that antibiotic resistance cases should not be overlooked during the consideration of topical antibacterial drugs usages especially most of the topical antibiotics which are available over the counter nowadays. In fact, pharmacists play an important role to prevent inappropriate use of over the counter topical antibiotics preparations [22-26].

Increase of bacterial resistance rate

Several studies have found that there was increasing resistance rate to mupirocin, fusidic acid, clindamycin, erythromycin, and tetracycline [27-30]. This is due to indiscriminate use of topical antibiotics [31,32]. Besides, Knobler's study stated that patient's inappropriate use of topical antibacterial drugs is one of the major factors in the development of bacterial resistance [12,32]. This again emphasized on the role and responsibilities of community pharmacists to counsel and educate patients in the correct usage of topical antibacterial drugs [31]. Moreover, Gollnick's study stated that topical antibiotic should be used less often and for short duration only to avoid the development of resistances [33]. It can be replaced with combination of topical antibiotics with topical retinoid, with benzoyl peroxide ointment (BPO), or with azelaic acid because these combinations claim to reduce the resistance rate and at the same time enhance the efficacy of acne

treatment [33]. This is further supported by Webster, author of Clinical Review of Acne Vulgaris, who said that use combination of clindamycin and benzoyl peroxide gel brings more benefits than using topical antibiotic alone. This review also mentioned that bacterial resistance happened more frequently with topical clindamycin and erythromycin. In addition, it is observed that combination of topical antibiotics with benzoyl peroxide is more useful than single topical antibiotics in the management of acne [34].

Lack of research on antibacterial resistance

Topical antibacterial drug is one of the over-the-counter products, but study specific to topical antibacterial drugs is lacking, and only little information about topical antibacterial drugs can be extracted from articles discussing OTC products. Besides, there are research articles which discussed about usage of antibiotics which includes both oral and topical antibiotics, but studies which only focus on topical antibiotics are limited even though several antibacterial agents have emerged over the years (Figure 1).

A study conducted in United Kingdom showed that topical antibiotics were the most purchased OTC products. Not only as over the counter products, topical antibacterial drugs also appear to be the most often requested prescription only medications (POM), followed by antibiotic-steroid combinations [35]. In addition to that, an observational study carried out in England found that the sales of topical chloramphenicol, a type of topical antibiotic had increased to 47.8 % within three years (2005 - 2007) after the product was made available over the counter [36].

Furthermore, a study carried out by National Center for Health Statistic (NCHS) also showed that topical antibacterial drugs combinations such as bacitracin, polymyxin/bacitracin as well as neomycin/polymyxin/bacitracin were listed as top twenty over the counter products for all physicians. In spite of that, the usage of the topical antibacterial drugs combinations mentioned was varied between dermatologists and non-dermatologists with 14.9 and 12.2 % respectively [11]. Moreover, a study carried out in the United States of America (USA) showed that dermatologists generally prescribed topical antibacterial drugs for conditions such as localized cutaneous bacterial infections, infected eczema, acne vulgaris, staphylococcal nasal carriage, postoperative prophylaxis of wound

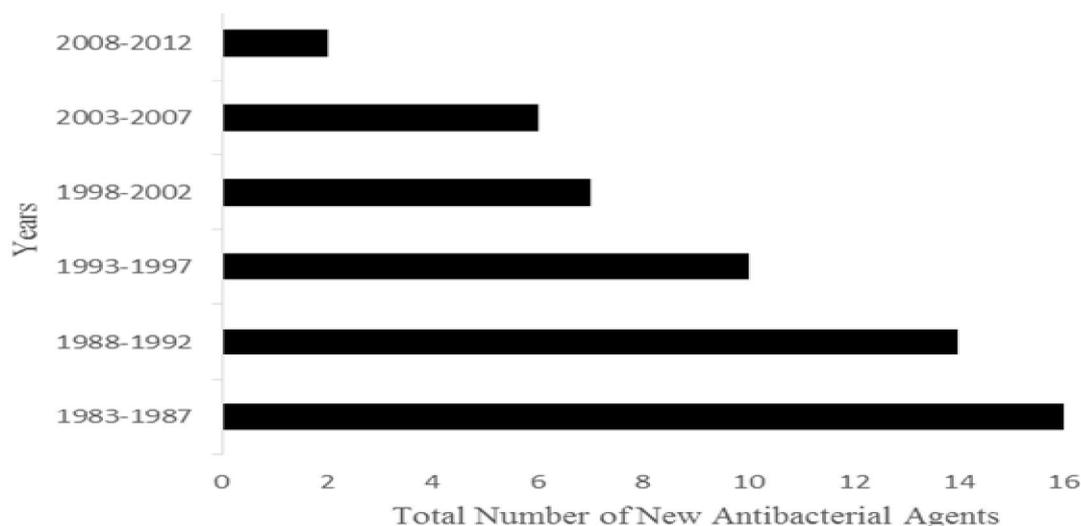


Figure 1: Research status in antibiotic development [40]

infections and chronic wounds, for instance ulcers [38].

CONCLUSION

Most of the studies on the usage of topical antibacterial have as their target population general practitioners, physicians and dermatologists, but only few studies has assessed whole communities. Antibacterial resistance ratio is also silently growing without any comprehensive measurements. Moreover, the studies focused on doctors. Based on the review evidence, hypothesis we are created and approached to convert the review hypothesis to research to ascertain the resistance occurrence of antibacterial utilization in Malaysia. Thus, further studies need to be conducted in Malaysia that specifically focus on community pharmacists. This is because available studies have not clearly pointed out the role of community pharmacists in dispensing, counselling, and educating the public on the usage of topical antibacterials; hence, this review hypothesis should test the community pharmacist contribution to the antibiotic usage pattern in the society.

ACKNOWLEDGEMENT

Authors would like to thank International Medical University, Malaysia for providing financial assistance for the conversion of this review hypothesis to research conversion {Project ID No:BP I-01/11(49)2014}.

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