Article type: Perspective

Formaldehyde as an alternative to antibiotics for treatment of refractory impetigo and other infectious skin diseases

Philip Nikolic[1], Poonam Mudgil[1]*, John Whitehall[1]

[1]School of Medicine, Western Sydney University, Campbelltown, NSW, Australia

*Corresponding author:
Poonam Mudgil

School of Medicine,

Western Sydney University,

Locked Bag 1797, Penrith,

NSW 2751, Australia

Phone: +612 4620 3945; Fax: +612 4620 3890

Email: p.mudgil@westernsydney.edu.au

Abstract

Introduction: Antibiotic resistant strains of bacteria are an increasing problem in hospitals and in the community. This has resulted in bacterial infections such as impetigo becoming difficult to treat. Alternative treatment options are needed.

Areas covered: In this paper a past study that assessed the health burden of scabies in North Queensland is described and from it the potential for formaldehyde as an alternative antimicrobial treatment is discussed. In doing so, antibiotic resistance, impetigo, permethrin and formaldehyde are introduced and the current understanding and limitations of the effects of formaldehyde on humans are outlined. The limited cases of formaldehyde resistance in bacteria is also discussed.

Expert opinion: Formaldehyde is currently used as a preservative in cosmetics and medicinal creams due to its antibacterial activity. It therefore has the potential to be used as an alternative antibacterial treatment for infections with antibiotic resistant bacteria. The harmful side effects of airborne formaldehyde and exposure in allergic individuals have been extensively studied. Significantly less research has been conducted on formaldehyde skin contact in healthy individuals. If formaldehyde is safe for topical use in humans, it has the potential to assist with combating antibiotic resistance.

Keywords: antibiotic resistance; formaldehyde; impetigo; methicillin resistance; permethrin; *Staphylococcus aureus*

Article highlights

- The increasing incidence of antibiotic resistant strains of *Staphylococcus aureus* has increased the need for alternative treatment options.
- Past work by Whitehall et al. [5] implicated treatment with a 5% permethrin cream as capable of curing infections with flucloxacillin resistant *S. aureus*.
- Permethrin is a synthetic pyrethroid that is used in the treatment of scabies infections but has been found to have no antibacterial effect, implicating the formaldehyde preservative of the cream in Whitehall et al. [5] as being responsible for the observed antibacterial activity.
- Formaldehyde is used in a wide variety of industries making it a ubiquitous indoor air pollutant that can cause a variety of harmful effects in humans including sensory irritation, carcinogenic effects in the respiratory system, allergic contact dermatitis and potentially increasing the rate of allergies and asthma in children.
- Despite the wealth of research on the effects of airborne formaldehyde and dermally applied formaldehyde in allergic individuals, there is significantly less available information on the effect of dermally applied formaldehyde in non-allergic individuals which is a major oversight in the literature.
- If formaldehyde can be confirmed to be minimally harmful to humans as a topically applied cream, it represents an alternative to traditional antibiotics for treating antibiotic resistant bacterial infections such as impetigo.

1. Introduction

The overuse and misuse of antibiotics has led to the development of antibiotic resistant strains of bacteria. These resistant strains have become a common problem in hospitals. Recently, in Australia, the incidence of community associated antibiotic resistance has been on the rise meaning that infections with resistant bacteria are no longer only occurring in hospitals, but also arising in the community [1]. One such bacterium that readily develops resistances to antibiotics is *Staphylococcus aureus*. *S. aureus* is a common skin commensal in humans but is also responsible for several infectious diseases, including skin and soft-tissue infections such as impetigo [2].

Impetigo and other infectious diseases generate significant disease burden and while current treatment options are mostly effective, more and more antibiotics are becoming unusable as more strains become resistant to them. It is therefore important that new treatment options that are effective against current resistant strains are identified, developed and used. It is also important that these new treatment options are capable of minimizing or preventing the ability for bacteria to develop resistance to them. This is why a substantial amount of research into new treatment options to combat resistant strains is currently being conducted. This is not limited to new antibiotics but also includes novel treatment options such as anti-virulence medication [3] and phage therapy [4]. Novel treatment options such as these are beneficial as it is less likely that bacteria will be able to develop resistance to them.

A prior study by Whitehall et al. [5] assessed the health burden associated with scabies and pyoderma in children at Mt Isa Hospital. The bacteria present in the infections and the treatment methods were also identified. Group A *streptococcus*, *S. aureus* and Group C *streptococcus* were present in the infected children and these infections were treated with soap baths, flucloxacillin, a 5% permethrin cream and an

adequate diet with iron supplementation as required. This was to cure both the scabies infections as well as the accompanying bacterial infections. What was interesting was that the patients all recovered despite most of the staphylococci strains being resistant to flucloxacillin. This implicates either the soap and water baths or the 5% permethrin cream as having a major benefit for treating antibiotic resistant bacterial infections.

Permethrin is a synthetic pyrethroid used in the treatment of scabies infections [6]. It targets the voltage sensitive sodium channels of the mites, inactivating them causing prolonged depolarization, paralysis and death [7]. While the effect of permethrin on insects is well characterized, the literature does not contain any mention of any antibacterial properties of permethrin and so our lab worked to identify if it was capable of targeting bacteria. For this, strains of methicillin resistant *S. aureus* and methicillin sensitive *S. aureus* were grown in the presence of a range of concentrations of permethrin. The degree of growth inhibition was determined using viable counts. After conducting these experiments and finding no inhibition in bacterial growth, our attention turned to another component of the 5% permethrin cream - the 0.3% formaldehyde preservative. Combination inhibition experiments were then conducted using the same strains in the presence of 5% permethrin and 0.3% formaldehyde together as well as individually. In these combination experiments, 0.3% formaldehyde was capable of completely inhibiting bacterial growth regardless of the presence of permethrin. Furthermore, the inability of 5% permethrin to inhibit bacterial growth was reinforced. It is therefore most likely that the antibacterial activity observed in Whitehall et al. [5] was a result of the formaldehyde preservative and not the permethrin itself.

If formaldehyde is effective in treating bacterial infections and safe for use in humans as a topical cream it represents a cheaper alternative to conventional antibiotic

therapy and would be especially useful in cases where conventional antibiotics have failed, such as refractory impetigo. Formaldehyde could therefore help to reduce the burden associated with antibiotic resistant bacteria. However, there are risks associated with the use of formaldehyde and these would need to be considered and, in some cases, investigated further to get more information than is currently available in the literature before it can be used in this manner.

2. Formaldehyde

Formaldehyde is the simplest aldehyde and exists as a colorless gas with a strong odor at room temperature. It was first synthesized in 1855 and is used for a variety of roles. This includes in embalming, the manufacture of particle-board, plywood and other wooden furniture products and as a preservative in products such as cosmetics and medicinal creams [8]. When used as a preservative it is used as an aqueous solution of 37%-50% formaldehyde called formalin [9]. Formaldehyde is used as a preservative due to its genotoxicity to bacteria and fungi. It is capable of binding to DNA and proteins to cause DNA-DNA cross-links, DNA-protein cross-links, irreversible formaldehyde adducts as well as other forms of DNA and protein damage [10,11]. It is effective against bacteria at very low concentrations with the MIC of formaldehyde against *S. aureus* being only 156 mg/L or 0.02% [12]. Formaldehyde has also been used to treat bacterial infections in the form of the antibiotic methenamine. Methenamine is an antibiotic that was used to treat urinary tract infections but has since become a "forgotten drug". It exerts its antibacterial activity by releasing formaldehyde in acidic environments and is capable of bactericidal activity at concentrations greater than 25 μg/ml [13].

Due to its wide use and presence in nature, formaldehyde is a common airborne pollutant. As such it primarily enters the body through the respiratory system. It can

also enter through ingestion and absorption through the skin. However, skin absorption of formaldehyde is considered to be poor [14,15]. Almost every body tissue has the ability to break down formaldehyde after absorption, converting it to the nontoxic formate [16].

The harmful effects of formaldehyde inhalation have been well reported in the literature leading to the development of guidelines to limit the allowed concentration of formaldehyde in the air. One such method to minimize the presence of airborne formaldehyde has been the use of formaldehyde releasing preservatives (such as Quaternium-15 and imidazolidinyl urea) rather than free formaldehyde. These formaldehyde releasing preservatives release formaldehyde slowly over time and this, in theory, allows for the concentration of formaldehyde present at any one time to remain low [17]. However, while much has been reported on the effects of airborne formaldehyde in humans, significantly less is available for dermal application of formaldehyde. Most of what is available is focused on the effects of formaldehyde in formaldehyde allergic individuals leading to allergic contact dermatitis with very little reported on the effect in non-allergic individuals. Furthermore, there are no *in vivo* human studies to identify the rate of formaldehyde absorption through the skin. This is despite the widespread use of formaldehyde in cosmetics and other products that regularly come into contact with the skin.

2.1. Formaldehyde as an airborne pollutant

Due to its generation by natural sources as well as its use in a variety of products, formaldehyde is a common indoor air pollutant. To minimize the potential for the adverse health effects associated with formaldehyde exposure, the World Health Organization (WHO) has developed an indoor air guideline for formaldehyde [18]. This was done as a result of the International Agency for Research on Cancer (IARC)

classification of formaldehyde as a human carcinogen in 2004 as well as the other harmful effects airborne formaldehyde can exert on humans present in the literature. The WHO guideline is based on a literature review that determined the effects of different concentrations of airborne formaldehyde on humans. This ranged from mild sensory irritation to the carcinogenic effects of formaldehyde and the key studies are summarized below.

Sensory irritation is generally defined as an unpleasant sensation in the eyes and airways, with eyes being more sensitive. Formaldehyde can cause sensory irritation and past studies have worked to identify the no observed effect level (NOEL) of formaldehyde. One such study was conducted on 21 individuals and consisted of a double blind random trial during which participants were exposed to various concentrations of formaldehyde [19]. Objective measurements of conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function, and reaction times were made before and after exposure to formaldehyde and used to evaluate the minimum concentrations required to exert irritation effects. This study found that eye irritation but not nasal irritation occurred at lower doses and the NOEL for formaldehyde exposure is 0.5 ppm for constant exposure and 0.3 ppm with peaks of 0.5 ppm for short term exposure (Table 1). This value is consistent with a past review presented by Paustenbach et al. of 150 scientific articles [20]. Odor may also cause some minor irritation and past studies indicate that this may be detected at or below 0.08 ppm [21,22].

In addition to causing these mild irritating effects, formaldehyde has been identified as a potential carcinogen with sufficient evidence that it can cause upper airway cancers in animals and nasopharyngeal cancer in humans as classified by the IARC. A cohort study of 25,619 plant workers who regularly came into contact with

formaldehyde was conducted that followed them from their year of employment (between 1934 and 1958) to December 31, 1994 [23]. The participants were divided into groups based on average formaldehyde exposure. An increased risk for death by nasopharyngeal cancer was supported for the highest concentrations of exposure (1 ppm to ≥ 4 ppm) (Table 1) and so for the purpose of airborne formaldehyde guidelines the WHO determined that formaldehyde exposure at or below 1 ppm does not induce excess nasopharyngeal cancer.

The above literature examples as well as much more ultimately lead to the WHO guideline of indoor formaldehyde levels to remain below 0.08 ppm and to not exceed that threshold for more than 30 minutes at a time. This guideline was recommended as it is sufficient to prevent both sensory irritation in the general population as well as the long-term adverse effects such as cancer [18].

2.2. The effect of formaldehyde exposure in children

As formaldehyde is near ubiquitous in the manufacture of common indoor products such as particle board, plywood and paneling, it represents a common indoor air pollutant that children are exposed to both in schools as well as at home. Children are more vulnerable to airborne toxic substances than adults as they have higher exposures per kilogram of body weight and because their respiratory system is not completely developed [24,25].

Studies have been conducted to understand the harmful effects of prolonged airborne formaldehyde exposure on children. An Australian study measured indoor formaldehyde levels in children's rooms and compared it with incidences of allergy and found that at higher formaldehyde exposure levels (still below local guidelines) children were at a higher risk of allergic sensitization [26]. A systematic review on the

association between formaldehyde exposure and childhood asthma pooled results from seven studies and indicated that children exposed to formaldehyde had a 3.5 times higher chance of having asthma [27]. Some potential mechanisms to explain this are also highlighted in the review. The first explanation was formaldehyde as an irritant being able to provoke mucosal inflammation in airways and produce cytokine mediators associated with asthma. Another explanation is formaldehydes ability to associate with larger protein molecules creating new antigenic moieties leading to the formation of specific IgE antibodies that can then bind mast cells causing their degranulation, inducing asthmatic responses. This production of IgE is also supported by Wantke et al. [28]. A more recent meta-analysis also concluded that formaldehyde exposure levels are higher in children with asthma than those without [29].

Recently however, Golden and Holm [30] raised concern that the associations seen between asthma and formaldehyde exposure may not be accurate as the chemical acrolein may be acting as an unrecognized confounder. Acrolein is capable of causing asthma and exists as an indoor air pollutant at levels higher than formaldehyde. Despite this, in prior studies looking at airborne contaminants and the development of asthma, acrolein was not considered. It may therefore have served as a confounder in these experiments and led to an overestimation of the association between formaldehyde and asthma.

2.3. The effect of dermal application of formaldehyde

Formaldehyde is a contact sensitizer that can cause allergic contact dermatitis in formaldehyde allergic individuals. In Europe the prevalence of formaldehyde allergy is 2-3% whereas in the United States it is 8-9%. However, in the 1980s the prevalence of formaldehyde sensitization was much higher with sensitization occurring in 18% of individuals in Japan. After government regulations restricted the levels of formaldehyde

permitted in underclothes this number dropped to 2.8%. This shows the importance of limiting prolonged formaldehyde exposure where possible [31]. It also shows the need for continued research into the effect of prolonged dermal contact with formaldehyde on the development of allergies and other harmful conditions.

Formaldehyde caused allergic contact dermatitis presents as red spots, swelling, irritation, pain and a burning sensation (Table 1). It can also appear as lesions with the potential for widespread eruptions on formaldehyde exposed skin [16,31]. Current EU regulations allow for up to 0.2% or 2000 ppm of formaldehyde to be present in cosmetics and household products. If the amount of formaldehyde present exceeds 0.05% (500 ppm) the label must have "contains formaldehyde" written on it [18]. However even formaldehyde at 500 ppm, can trigger allergic contact dermatitis in formaldehyde allergic individuals (Table 1) [32]. Formaldehyde allergies are diagnosed using a patch test. A 1% formaldehyde solution is used as standard but this test is often criticized for its high number of false positives (< 50% of positives are reproducible) [33] and false negatives [31].

While there is a substantial amount of research conducted on the effect of formaldehyde in allergic individuals, there is significantly less published about the effect of formaldehyde in healthy, non-allergic individuals. A majority of the available information was published in the late 80s. For example, two papers that deal with the topic of dermal contact of formaldehyde outside of allergic reactions are presented by Nair et al. [34] and Iversen [35] (Table 1). The former article details a trial study to test whether a 0.25% formalin spray was suitable for use in the treatment of burns in terms of the generation of eschar and the minimizing of bacterial infection. The spray was capable of assisting with the healing process by reducing the risk of infection. The latter article investigated whether topical applications of formaldehyde would lead to the

generation of cancerous growths in mice. On its own, formaldehyde did not induce tumor growth but did decrease latency time in induced carcinogenesis. The observed result in Iversen [35] was then supported by another study by Iversen [36] that repeated the same experiment but on SENCAR mice (which are more sensitive to chemical tumorigenesis) with similar results being observed (Table 1).

A more recent study on the effects of dermal formaldehyde exposure was conducted by Saito et al. [37]. In this study the irritant effects of dermally applied formaldehyde to mice ears was investigated (Table 1). 2%, 5% and 10% solutions of formaldehyde caused ear swelling and the peak response increased with the concentration of formaldehyde. The expression of IL-4 was also increased. This study further confirmed the irritant activity of dermally applied formaldehyde but is limited in that the minimal concentration required for the induction of irritation was not identified.

In addition to the limited study on the effect of dermally applied formaldehyde on human skin there is limited available literature on the rate of formaldehyde absorption through skin. No *in vivo* studies in humans have been conducted on the rate of absorption of formaldehyde through skin but some information is available using animals and excised human skin. One such animal study applied a cream containing radioactively tagged formaldehyde (0.1%) to the skin of rats [14]. At the end of the study no more than 5% of the applied formaldehyde was absorbed through the skin (Table 1).

Another animal study tested formaldehyde absorption on rats, guinea-pigs and monkeys [38]. No accumulation of formaldehyde was found in any tissue with the majority of formaldehyde found in the air (Table 1). The skin of monkeys was less permeable to formaldehyde than the skin of rodents and a majority of formaldehyde was lost to evaporation.

An experiment that used excised human skin tested absorption of both a formalin solution of 37% formaldehyde and 10% formaldehyde in phosphate buffer [15]. Skin absorption of formaldehyde occurred at 319 (for the formalin solution) and 16.7 (for the phosphate buffer solution) micrograms per square centimeter per hour (Table 1).

These results indicate that formaldehyde is poorly absorbed through undamaged skin. Furthermore, as mentioned above, the human body is capable of breaking down formaldehyde into the non-toxic formate. When taken together, harmful systemic effects of dermal formaldehyde exposure are unlikely. This is supported by the lack of formaldehyde accumulation in tissue as reported in Jeffcoat, Chasalow and Feldman [38]. However conducting *in vivo* studies on humans looking for the rate of absorption of formaldehyde through unbroken skin as well as any potential harmful effects from prolonged exposure would be reassuring given it is a common preservative in cosmetics and other dermally applied products. Such studies are however absent from the literature.

2.4. Formaldehyde resistance in bacteria

In addition to its wide use in manufacturing and as a preservative, formaldehyde is also an important cellular metabolite in the metabolism of methylated compounds in methylotrophic bacteria. It is generally produced by methanotrophic and methyltrophic bacteria during oxidation of hydrocarbons such as methane and methanol [10]. As a result, bacteria have developed methods to tolerate the toxic effects of formaldehyde. This has been primarily through the enzymatic breakdown of formaldehyde into less toxic products. One such method is found in *Amycolatopsis methanolica* and *Mycobacterium gastri* in the form of a formaldehyde dismutase that breaks formaldehyde down into formate and methanol. However, both species are still

susceptible to formaldehyde at concentrations above 0.8mM [39].

Formaldehyde resistance has been reported in *Pseudomonas* species and in the family *Enterobacteriaceae*. In *Enterobacteriaceae*, resistance developed as a result of plasmid acquisition while in *Pseudomonas*, resistance is chromosomally located. The resistances are due to the presence of formaldehyde dehydrogenase enzymes. Nicotinamide adenine dinucleotide (NAD) dependent formaldehyde dehydrogenases are found in methanol-utilizing methylotrophic bacteria like *Pseudomonas methanica* and some other formaldehyde-utilizing bacteria like *Pseudomonas aeruginosa*. As these species utilize formaldehyde it is essential that they are capable of surviving its presence. Strains of *Escherichia coli* resistant to formaldehyde have also been commonly found and it is accepted that resistance to formaldehyde is most often found in gram-negative bacteria [40]. Formaldehyde resistant strains of *S. aureus* have not been reported in the literature.

3. Impetigo

Impetigo is a skin infection that is most commonly found in children and can be caused by either *S. aureus* or *Streptococcus pyogenes*. Impetigo contributes to a high burden of disease in resource poor communities with an estimated global burden of 162 million children in low to low-middle income countries being affected by impetigo at any one time. In Australia alone, it is estimated that over 15,000 indigenous children suffer from impetigo at any one time [41]. The human skin barrier is usually capable of preventing bacteria from causing impetigo. However, if this protective layer is compromised, by conditions such as chickenpox and scabies or through damage caused by scratching or surgery, bacteria can invade and colonize, leading to the development of impetigo.

Impetigo presents in three main forms and is primarily caused by *S. aureus*. The first, called non-bullous impetigo presents as a maculopapular lesion that becomes a

thin-walled vesicle. The vesicle ruptures and dries as a yellowish crust. The second presentation, called bullous impetigo presents as small vesicles at first that then become localized blisters. These blisters do not rupture as easily as the vesicles in non-bullous impetigo. The final presentation of impetigo is called ecthyma. Ecthyma extends further into the dermis layer than the other two forms, and is characterized by vesicles that rupture producing circular ulcers with black-brown crusts. All three forms can also be caused by *S. pyogenes* but this is less common [42].

Impetigo is usually treated with topical antibiotic creams but if the infection is more severe, or is a case of refractory impetigo, an oral antibiotic will be administered instead. The first choice creams for topical treatment of impetigo are fusidic acid and mupirocin. The use of a topical cream is preferred to an oral antibiotic as it results in fewer side effects [42]. Strains of *S. aureus* resistant to two common antibiotics used for the treatment of impetigo, fusidic acid [43] and mupirocin, [44] have been reported. This growing resistance has led to the use of retapamulin as an alternative treatment option [45].

4. Conclusion

Currently many clinically important strains of bacteria are resistant to antibiotics with some even resistant to what were considered to be last resort antibiotics. If something is not done, we may enter the post antibiotic era where infections that were once easy to treat become untreatable. This would increase both the number of deaths from bacterial infections as well as the burden of cost associated with extended hospital stays. Formaldehyde has been implicated in a prior study as being able to decrease infection by antibiotic resistant bacteria when applied as a cream. Furthermore, it is already used in cosmetics and medicinal creams as a preservative. It is therefore capable of killing bacteria and is safe to be used in humans at controlled concentrations. The available

literature indicates that formaldehyde is poorly absorbed through the skin and it is difficult for bacteria to develop resistance to it. With further research into its prolonged effect on humans after topical application, formaldehyde may represent an antimicrobial capable of alleviating the burden associated with antibiotic resistance and help to treat infections that may otherwise be untreatable.

5. Expert opinion

Treatment of bacterial infections has in the past been done irresponsibly. This is both in terms of the prescription of antibiotics when unnecessary and the prescription of broad spectrum antibiotics when a narrower spectrum would have sufficed. As a result of this overuse and misuse of antibiotics, antibiotic resistant strains of bacteria have become a major threat both in hospitals and in the wider community. New treatment options are needed as more and more antibiotics become ineffective. However, increased antibiotic development will not solve the problem of resistance as new resistances can and will always develop. Novel methods that are harder or even impossible for bacteria to develop resistance against are needed along with responsible treatment practices.

Formaldehyde with its genotoxic effects against bacteria is already used as a preservative in cosmetics and medicinal creams and as the active ingredient in the antibiotic methenanime. It is also very difficult for gram positive bacteria to develop resistance to formaldehyde. Formaldehyde therefore represents a promising potential alternative treatment option for infections with antibiotic resistant bacteria. However, in order for formaldehyde to be used as an antibacterial, its harmful effects on humans would need to be taken into account. This is however made difficult by the absence of key information in the literature.

Formaldehyde has been extensively studied in terms of the risks it poses as an airborne pollutant. Its effect on allergic individuals after skin contact has also been

studied and reported in the literature. However, the potential negative effects of dermally applied formaldehyde in non-allergic individuals has not been studied nearly as rigorously. Nor has the rate of skin absorption in humans with no *in vivo* human studies conducted. What little information is available is over 30 years old and for a chemical as ubiquitous as formaldehyde this is concerning. If there is so much regulation and research done on the harmful effects of airborne formaldehyde, then why is there not nearly as much available for dermally applied formaldehyde? Either it is not as dangerous in this form or it is an oversight. Either way it represents a worrying absence in the literature and a potential avenue for future research.

The currently available literature, though old, does indicate that dermally applied formaldehyde is poorly absorbed by undamaged skin and that what little is absorbed is rapidly detoxified with little to no spread to organs. When this is combined with the continued use of low concentrations of formaldehyde in dermally applied products, it would appear that minimal dermal application of formaldehyde is safe for use in non-allergic humans. Before formaldehyde can be recommended for use as a novel antibacterial for treatment of infections with antibiotic resistant bacteria however, there is a need for more in depth research into the effects of dermally applied formaldehyde. If, after further research is conducted, the results of past studies are confirmed along with a confirmation that the application of a cream containing formaldehyde does not cause harm to the patient, does not increase their chance of developing cancer, does not increase airborne formaldehyde concentration above hazardous levels, is not absorbed at toxic levels, does not contribute to the development of asthma and does not facilitate the development of a formaldehyde allergy, it could be used to treat infectious diseases. For example, it could be used in situations where traditional antibiotics have failed (such as refractory impetigo) as a new treatment

option. If done so it will be able to treat bacterial infections that have become untreatable as a result of the rise of antibiotic resistance. Though limited, the available literature does indicate that formaldehyde would be suitable for use in this manner.

Formaldehyde also opens itself to help reduce the cost of treatment for some diseases. For example, in scabies infections an insecticide is needed to treat the scabies mite infection and an antibiotic is needed to treat the secondary bacterial infections. If formaldehyde is suitable for the treatment of bacterial infections in humans, rather than treating scabies and the accompanying secondary bacterial infections with two separate medicines, a single insecticide cream with a formaldehyde preservative would suffice.

Formaldehyde has the potential to help alleviate the problems associated with antibiotic resistance but without further research into the safety of formaldehyde use in humans, it cannot be recommended for use in this way. Therefore, it is essential that in the near future research is conducted on the effects that dermal formaldehyde application exerts when applied on humans.

As infections with antibiotic resistant strains of *S. aureus* have reached epidemic levels all over the world, new antibiotics and new novel treatment options are needed [46]. Formaldehyde represents just one potential weapon to fight back against antibiotic resistance. If these new treatment options are found and used responsibly the threat antibiotic resistance poses can begin to be reversed. However, if effective treatments are not found, we may very well enter the post-antibiotic era.

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest

(1) Antimicrobial Use and Resistance in Australia. Second Australian report on antimicrobial use and resistance in human health. Sydney: Australian Commission on Safety and Quality in Health Care; 2017.

(2) Rojo P, Barrios M, Palacios A, et al. Community-associated Staphylococcus aureus infections in children. Expert Rev Anti Infect Ther. 2010;8(5):541-554.
*Review showing the increasing incidence of community associated MRSA infections.

(3) Khodaverdian V, Pesho M, Truitt B, et al. Discovery of antivirulence agents against methicillin-resistant Staphylococcus aureus. Antimicrob Agents Chemother. 2013;57(8):3645-3652.

(4) Zhang G, Zhao Y, Paramasivan S, et al. Bacteriophage effectively kills multidrug resistant Staphylococcus aureus clinical isolates from chronic rhinosinusitis patients. Int Forum Allergy Rhinol. 2018;8(3):406-414.

(5) Whitehall J, Kuzulugil D, Sheldrick K, et al. Burden of paediatric pyoderma and scabies in North West Queensland. J Paediatr Child Health. 2013;49(2):141-143.
**The results in this paper were the starting point for the hypothesis that formaldehyde may be used to treat bacterial infections.

(6) Currie BJ, McCarthy JS. Permethrin and ivermectin for scabies. New Engl J Med. 2010;362(8):717-725.

(7) Andriantsoanirina V, Izri A, Botterel F, et al. Molecular survey of knockdown resistance to pyrethroids in human scabies mites. Clin Microbiol Infect. 2014;20(2):139-141.

(8) Salthammer T. The formaldehyde dilemma. Int J Hyg Environ Health. 2015;218(4):433-436.
*A commentary on the sources of airborne formaldehyde and the concerns associated with it.

(9) Montanaro A. Formaldehyde in the workplace and in the home: exploring its clinical toxicology. Lab Med. 1996;27(11):752-757.

(10) Chen NH, Djoko KY, Veyrier FJ, et al. Formaldehyde stress responses in bacterial pathogens. Front Microbiol. 2016;7:257.

(11) Nielsen GD, Larsen ST, Wolkoff P. Re-evaluation of the WHO (2010) formaldehyde indoor air quality guideline for cancer risk assessment. Arch Toxicol. 2017;91(1):35-61.
**A comprehensive review of formaldehyde and the WHO guidelines and the validity of the set indoor air guidelines.

(12) Mazzola PG, Jozala AF, Novaes LCDL, et al. Minimal inhibitory concentration (MIC) determination of disinfectant and/or sterilizing agents. Braz J Pharm Sci. 2009;45(2):241-248.

(13) Lo TS, Hammer KDP, Zegarra M, et al. Methenamine: a forgotten drug for preventing recurrent urinary tract infection in a multidrug resistance era. Expert Rev Anti Infect Ther. 2014;12(5):549-554.
*A report giving an example of an antibiotic that uses formaldehyde to kill bacteria

(14) Bartnik FG, Gloxhuber C, Zimmermann V. Percutaneous absorption of formaldehyde in rats. Toxicol Lett. 1985;25(2):167-172.

(15) Lodén, M. The in vitro permeability of human skin to benzene, ethylene glycol, formaldehyde, and n-hexane. Acta Pharmacol Toxicol. 1986;58(5):382-389.

(16) Kim KH, Jahan SA, Lee JT. Exposure to formaldehyde and its potential human health hazards. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2011;29(4):277-299.

(17) Moennich JN, Hanna DM, Jacob SE. Formaldehyde-releasing preservative in baby and cosmetic products: health risks related to exposure during infancy. J Dermatol Nurses Assoc. 2009;1(3):211-214.

(18) World Health Organization. WHO guidelines for indoor air quality: selected pollutants. Denmark: WHO Regional Office for Europe;2010.
*The current guidelines for indoor levels of airborne pollutants including formaldehyde

(19) Lang I, Bruckner T, Triebig G. Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. Regul Toxicol Pharmacol. 2008;50(1):23-36.

(20) Paustenbach D, Alarie Y, Kulle T, et al. A recommended occupational exposure limit for formaldehyde based on irritation. J Toxicol Environ Health Part A. 1997;50(3):217-264.

(21) Berglund B, Nordin S. Detectability and perceived intensity for formaldehyde in smokers and non-smokers. Chem Senses. 1992;17(3):291-306.

(22) Cain WS, Schmidt R, Wolkoff P. Olfactory detection of ozone and d- limonene: reactants in indoor spaces. Indoor Air. 2007;17(5):337-347.

(23) Hauptmann M, Lubin JH, Stewart PA, et al. Mortality from solid cancers among workers in formaldehyde industries. Am J Epidemiol. 2004;159(12):1117-1130.

(24) Bradman A, Gaspar F, Castorina R, et al. Formaldehyde and acetaldehyde exposure and risk characterization in California early childhood education environments. Indoor Air. 2017;27(1):104-113.

(25) Oliveira M, Slezakova K, Delerue-Matos C, et al. Indoor air quality in preschools (3- to 5-year-old children) in the Northeast of Portugal during spring-summer season: pollutants and comfort parameters. J Toxicol Environ Health Part A. 2017;80(13-15):740-755.

(26) Garrett MH, Hooper MA, Hooper BM, et al. Increased risk of allergy in children due to formaldehyde exposure in homes. Allergy. 1999;54(4):330-337.

(27) McGwin G Jr, Lienert J, Kennedy JI Jr. Formaldehyde exposure and asthma in children: a systematic review. Environ Health Perspect. 2010;118(3):313-317.

(28) Wantke F, Demmer CM, Tappler P, et al. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children. Clin Exp Allergy. 1996;26(3):276-280.

(29) Yao Y, Liang W, Zhu L, et al. Relationship between the concentration of formaldehyde in the air and asthma in children: a meta-analysis. Int J Clin Exp Med. 2015;8(6):8358-8362.

(30) Golden R, Holm, S. Indoor air quality and asthma: has unrecognized exposure to acrolein confounded results of previous studies?. Dose Response. 2017;15(1):e1559325817691159.

(31) De Groot AC, Flyvholm MA, Lensen, G, et al. Formaldehyde- releasers: relationship to formaldehyde contact allergy. Contact allergy to formaldehyde and inventory of formaldehyde- releasers. Contact Derm. 2009;61(2):63-85. **A comprehensive review on formaldehyde and formaldehyde releasers and how they affect allergic individuals

(32) Hauksson I, Pontén A, Isaksson M, et al. Formaldehyde in cosmetics in patch tested dermatitis patients with and without contact allergy to formaldehyde. Contact Derm. 2016;74(3):145-151.
*A study showing how often formaldehyde or formaldehyde releasers are found in cosmetics and how these (even within regulation levels) can affect formaldehyde allergic individuals.

(33) Carlsen BC, Menné T, Johansen JD. 20 Years of standard patch testing in an eczema population with focus on patients with multiple contact allergies. Contact Derm. 2007;57(2):76-83.

(34) Nair RG, Supe AN, Samsi AB. Formalin (0.25%) as topical anti-microbial agent in burns. J Postgrad Med. 1991;37(1):1-4.

(35) Iversen OH. Formaldehyde and skin carcinogenesis. Environ Int. 1986;12(5):541-544.

(36) Iversen OH. Formaldehyde and skin tumorigenesis in SENCAR mice. Environ Int. 1988;14(1):23-27.

(37) Saito A, Tanaka H, Usuda H, et al. Characterization of skin inflammation induced by repeated exposure of toluene, xylene, and formaldehyde in mice. Environ Toxicol. 2011;26(3):224-232.

(38) Jeffcoat AR, Chasalow F, Feldman DB. Disposition of [14C] formaldehyde after topical exposure to rats, guinea pigs, and monkeys. In: Gibson GE, editor. Formaldehyde toxicity. New York (NY): Hemisphere Publishing; 1983. p. 38-49.

(39) Bystrykh LV, Govorukhina NI, van Ophem PW, et al. Formaldehyde dismutase activities in gram-positive bacteria oxidizing methanol. Microbiology. 1993;139(9):1979-1985.

(40) Kümmerle N, Feucht HH, Kaulfers PM. Plasmid-mediated formaldehyde resistance in Escherichia coli: characterization of resistance gene. Antimicrob Agents Chemother. 1996;40(10):2276-2279.

(41) Bowen AC, Mahé A, Hay RJ, et al. The global epidemiology of impetigo: a systematic review of the population prevalence of impetigo and pyoderma. PLoS ONE. 2015;10(8):e0136789.

(42) Ghazvini P, Treadwell P, Woodberry K, et al. Impetigo in the pediatric population. J Dermatolog Clin Res. 2017;5(1):1092.

(43) Alsterholm M, Flytström I, Bergbrant IM, et al. Fusidic acid-resistant Staphylococcus aureus in impetigo contagiosa and secondarily infected atopic dermatitis. Acta Derm Venereol. 2010;90(1):52-57.
(44) Poovelikunnel T, Gethin G, Humphreys H. Mupirocin resistance: clinical implications and potential alternatives for the eradication of MRSA. J Antimicrob Chemother. 2015;70(10):2681-2692.
(45) Pereira LB. Impetigo – review. An Bras Dermatol. 2014;89(2):293-299.
(46) Chambers HF, DeLeo FR. Waves of resistance: Staphylococcus aureus in the antibiotic era. Nat Rev Microbiol. 2009;7(9):629-641.
(47)