HHS Public Access

Author manuscript

Curr Pharm Des. Author manuscript; available in PMC 2021 December 15.

Published in final edited form as:

Curr Pharm Des. 2015 ; 21(16): 2089–2100. doi:10.2174/1381612821666150310104416.

Repurposing non-antimicrobial drugs for treatment of staphylococcal infections

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Abstract

The development and approval of new antimicrobials capable of being used to treat infections caused by multidrug-resistant pathogens has not kept pace with the rapid emergence of bacterial resistance. Without a doubt, there is a critical unmet need for the identification of novel strategies to develop antimicrobials to deal with this new scourge. One strategy, which warrants special attention as a unique method for identifying new antimicrobials, is drug repurposing. Several approved drugs have been successfully repurposed for different ailments giving hope that this strategy can also be utilized to uncover new antibacterials. To aid in this process, the present review presents approved drugs, which have been shown to possess antimicrobial activity against *Staphylococcus aureus* and their potential clinical applications. Additionally, approved drugs with novel applications such as interference in staphylococcal pathogenesis and host immunomodulators are also explained. The current review also discusses the challenges associated with repurposing approved drugs as antibacterials and potential uses of approved drugs that can be further explored to develop these existing drugs as novel therapeutics to treat multi-drug resistant staphylococcal infections. Collectively, the information presented demonstrates that repurposing approved drugs as antimicrobials may help to speed up the drug development process and save years of expensive research invested in antimicrobial drug development.

Keywords

Repurposing; non-antibiotics; multidrug-resistance; staphylococci; MRSA; virulence factors; bacterial resistance; immunomodulatory agents

1. Introduction

Bacterial resistance to conventional antibiotics is a burgeoning global health epidemic that necessitates urgent action. Reports by the Centers for Disease Control and Prevention in the United States and the European Centre for Disease Control and Prevention indicate more than two million individuals in the United States and nearly 400,000 individuals in Europe are stricken each year with infections caused by multidrug-resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-

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resistant *Klebsiella pneumonia* (KPC) and vancomycin-resistant *Enterococcus faecium* (VRE) [1, 2]. Treatment of these infections are often expensive costing residents an estimated $55 billion in the United States and €1.5 billion in the European Union in total costs every year [1, 2]. Furthermore, the issue of bacterial resistance to antibiotics around the world appears to be getting worse with the emergence of pathogens exhibiting resistance to agents of last resort (including glycopeptides, oxazolidinones, and carbapenems) [3-5]. Even more alarming, the development and approval of new antimicrobials capable of being used to treat infections caused by multidrug-resistant pathogens has not been able to keep pace with the rapid emergence of bacterial resistance to currently efficacious antibiotics. Drug development of novel compounds is a time-consuming, costly, and high-risk venture given that few compounds successfully make it through stringent regulatory requirements to reach the marketplace. Collectively, this points to a critical need for the identification of novel strategies to develop antibiotics to deal with this challenging health issue. One strategy, which warrants more attention as a unique method for identifying new antimicrobials, is drug repurposing.

Drug repurposing is a clever strategy to identify new applications (“off” targets) for drugs approved for other clinical diseases [6]. This strategy has been successfully employed to unearth new potential treatment options for different diseases including cancer, amyotrophic lateral sclerosis (ALS), Alzheimer’s disease, and malaria [7]. On average, 20-30 new drugs receive FDA-approval each year; of these, 30% are repurposed agents [8, 9]. Thus, this points to repurposing being a quicker strategy to stock the drug discovery pipeline, particularly for antibiotics, compared to the traditional process of *de novo* synthesis of new compounds which can cost pharmaceutical companies $800 million to upwards of $1 billion in research and development expenditures and require 10-17 years to attain regulatory approval [10, 11]. Repurposing existing approved drugs permits companies to bypass much of the preclinical work and early stage clinical trials required for new compounds (particularly toxicological and pharmacological analysis of drugs) thus cutting into the cost (by nearly 40%) associated with bringing a drug to the marketplace [10].

In addition to lower drug discovery-associated costs, repurposing approved drugs (particularly for identification of new antibiotics) has several additional benefits. Given these drugs have already been tested in human patients, valuable information pertaining to pharmacokinetic and pharmacodynamic parameters are known [7]. This permits a better understanding of the overall pharmacology of the drug, potential routes of administration (i.e. systemic versus local applications), and establishing an appropriate dosing regimen for patients. Moreover, as the toxicity profile of these drugs in humans has been extensively studied, valuable information has already been obtained regarding potential adverse side effects present with using the drug at certain therapeutic doses. This information is important as it pertains to antimicrobials as the concentration where toxicity is observed with host tissues can be correlated with the minimum inhibitory concentration (MIC) values obtained in standard bacterial susceptibility assays to determine if drugs are viable candidates for repurposing as antimicrobials.

Interestingly, several approved drugs for different ailments that have been successfully repurposed as anti-infective agents especially to treat parasitic and protozoal diseases (Table

1). However, to date, not a single drug has been successfully repurposed for use as an antibacterial, particularly for hard-to-treat infections caused by bacteria such as *S. aureus*. Hence, given the significant problem posed by pathogenic bacteria, more effort and attention needs to be focused on using drug repurposing as a tool to uncover new treatment options for infections caused by multi-drug resistant pathogens, such as *S. aureus*. To aid in this process, the present review will delve into approved drugs which have demonstrated promise to be repurposed as agents for *S. aureus* infections, discuss alternative applications for drugs possessing antimicrobial activity, and address current limitations to expedite the discovery and development of approved drugs to be repurposed for use as antibiotics.

2. Approved non-antimicrobial drugs with activity against *S. aureus*

Several studies have presented approved non-antibiotic drugs that possess antimicrobial activity, especially against *S. aureus*, indicating these drugs have potential alternative use for treatment of staphylococcal infections. However, the major hindrance for repurposing these drugs pertains to a lack of *in vivo* studies to confirm these drugs do possess antibacterial activity in an animal model. The primary criteria for *in vivo* systemic studies pertain to the availability of enough free drug in the plasma, when given at the clinical dose, to ensure inhibition of bacterial growth. Hence considering the human plasma concentration of the non-antimicrobial drugs, hereby we classify the antimicrobial activity of approved and clinically-safe non-antibiotic drugs into two categories (a) drugs with activity in a clinical range that can be achieved systemically and (b) drugs with activity that cannot be achieved systemically (Table 2).

2.1. Drugs with activity in a clinical range that can be achieved systemically

Several of the approved drugs discussed below have antimicrobial activity (denoted as the minimum inhibitory concentration (MIC) or lowest concentration of drug capable of inhibiting bacterial growth) several folds lower than the plasma concentration of the drug in humans. Therefore these particular drugs might be potential candidates to consider for treatment of systemic staphylococcal infections.

2.1.1. Auranofin—Auranofin, a FDA-approved gold compound has been used for treating rheumatoid arthritis for almost 30 years [12, 13]. However, its exact mechanism of action (MOA) in treating rheumatoid arthritis still remains unclear [14, 15]. Interestingly, independent of its anti-rheumatoid action, auranofin has also been shown to have anti-parasitic effects. .Of particular interest, is the recent discovery of auranofin's efficacy in treatment of human amebiasis caused by *Entamoeba histolytica.* Auranofin exhibited anti-Entamoeba activity with a half-maximal effective concentration (EC_{50} = concentration of drug necessary to reduce the culture density to 50%) of 0.338 μg/ml. The EC_{50} for *E. histolytica* was seven-fold lower than the clinically achievable blood concentration of the drug (2.37 μg/ml). Even though auranofin is rapidly metabolized and 60% is bound to plasma proteins, it was found to be effective in two animal models of amebic colitis and amebic liver abscess [16, 17]. Based on these studies, auranofin was granted orphan-drug status from the FDA for treatment of human amebiasis in 2012 [16].

With regards to auranofin's antibacterial activity, two recent studies have demonstrated that auranofin also possesses potent antimicrobial activity against *S. aureus* [18, 19]. The *in vitro* MIC reported for this drug ranges from 0.125 to 0.5 μg/ml [18, 19]. More importantly, auranofin demonstrated bactericidal activity against several multidrug-resistant *S. aureus* within an achievable clinical drug concentration in humans [16, 18, 19]. Based on these promising preliminary studies, and its recent approval by the FDA as an anti-amoebic drug, auranofin might be a potential agent to repurpose for the treatment of systemic and topical staphylococcal infections. However, future studies are needed to reveal its mechanism of action against *S. aureus* and establish its antibacterial activity *in vivo* in different animal models of *S. aureus* infection.

2.1.2. Ebselen—Ebselen, an organoselenium compound also known as PZ51 or DR3305, has been widely investigated for its anti-inflammatory, anti-atherosclerotic and antioxidative properties [20-23]. This particular non-approved but clinically safe drug has a well-studied toxicology and pharmacology profile and is currently undergoing clinical trials as a treatment option for different ailments including arthritis, cardiovascular disease, stroke, atherosclerosis, cancer and bipolar disorder [21, 24-27]. In addition to being used as a treatment for multiple diseases, ebselen has also been shown to possess potent antimicrobial activity *in vitro* [28, 29]. It has antimicrobial activity against yeast and *Escherichia coli* and by interfering with proton-translocation and inhibiting the thioredoxin reducatse (TrxR) enzyme respectively [29, 30]. Another interesting study has shown that it has potent antimicrobial activity against *S. aureus* with a MIC of 0.20 μg/ml [28]. This MIC is several folds lower than the plasma concentration (4-6μg/ml) of the drug. [31]. Considering its potent anti-staphylococcal activity in vitro, studies on the antibacterial MOA of ebselen and evaluating its activity *in vivo* against *S. aureus* could be useful for developing ebselen as an antibacterial agent to treat multidrug-resistant staphylococcal infections [28, 29].

2.1.3. 5-fluoro-2'-deoxyuridine—Antimetabolite such as 5-fluoro-2'-deoxyuridine (FdUrd) belong to a class of antineoplastic drugs which is used for treatment of various malignant diseases [32]. They primarily act by inhibiting DNA and RNA synthesis [32]. In addition to their anticancer activity, this drug also exhibit potent antimicrobial activity below the concentration that can be achieved in human plasma [33]. FdUrd, is capable of inhibiting *S. aureus* growth at a MIC ranging from 0.0007-0.002 μg/ml, which is several hundred folds lower than the mean plasma concentration of 14.1 ±2.7 μg/ml [34-36]. In addition, FdUrd is a pro-drug which needs the deoxyribonucleoside kinase (dNK) enzyme to exert its action; this enzyme is present in *S. aureus* [35, 36]. Hence, considering promising *in vitro* antibacterial studies conducted this far, FdUrd warrant further evaluation as anti-staphylococcal drugs. Future studies would need to be conducted to test their *in vivo* antibacterial efficacy in different animal models.

2.2. Drugs with activity that cannot be achieved systemically

Most of the approved non-antimicrobial drugs that possess anti-staphylococcal activity have MIC values that are higher than their plasma concentration; thus, using these drugs for treatment of systemic infections might not be a viable option. However, they can be used for topical application for treating staphylococcal skin infections. Community-associated

methicillin-resistant *S. aureus* (CA-MRSA) strains have become a significant source of staphylococcal skin infections. In particular, the strain MRSA USA300 has emerged as one of the most highly prevalent isolates in United States responsible for skin and soft tissue infections [37, 38]. In addition to CA-MRSA, Panton-Valentine leukocidin (PVL), a cytotoxin producing strains of *S. aureus* are of serious problem which also causes tissue necrosis in the skin and lungs [39]. Moreover, MRSA colonization in the skin and mucosa is considered an important risk factor for invasive infections [40]. Thus repurposing approved drugs, with high MIC values that cannot be achieved systemically, for use to treat MRSA skin infection and as decolonizing agents is a sensible approach, which warrants further investigation. These drugs can be either used as single agents or can be combined with conventional antimicrobials to enhance the efficacy and extend the life span of traditional antimicrobials. Furthermore, several of these drugs have additional benefits that will permit their use as a topical antimicrobial agent. For example, the drugs simvastatin and celecoxib have been shown to inhibit the pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and IL-6 [41, 42]. Controlling excess inflammation, particularly by limiting TNF-α and IL-6 production, in chronic wounds plays a beneficial role in wound healing [43-48]. Additionally, simvastatin has been shown to enhance wound healing and angiogenesis in diabetic mice [49]. Hence, taking into account the antimicrobial activities of these agents combined with their beneficial properties (such as anti-inflammatory properties), further investigation is warranted to test these approved drugs in topical for topical treatment of MRSA skin infections in animal models.

3. Novel uses of approved drugs

For the past few decades, the development of new antimicrobials has slowed down while the evolution of bacterial resistance has continued to rise; hence, there is an urgent need to identify alternative strategies to combat infections caused by multidrug-resistant *S. aureus* [50-52]. Emergent approaches that have drawn great interest recently include drugs with indirect antimicrobial activity which work by (i) targeting virulence factors and toxins (anti-virulence agents) [51, 53, 54], (ii) enhancing host immunity (immunomodulators) [52, 55], and (iii) enhancing entrance of other antimicrobials into target cells by increasing the permeability of the outer membrane or by inhibiting efflux pumps (helper drugs) [56]. These novel approaches can be combined with traditional antibiotics to enhance the efficacy and extend the life span of antimicrobial drugs and to minimize the evolution of bacterial resistance to these agents. Here we provide several examples of FDA-approved non-antimicrobial drugs, which do not have direct antimicrobial activity or have very high MIC *in vitro* that cannot be achieved clinically; though they cannot be used systemically, they have potential for use to disrupt bacterial pathogenesis or to modulate a host's immune response to combat staphylococcal infections.

3.1. Targeting virulence factors

Targeting staphylococcal virulence factors and toxins is an important strategy to disarm the pathogen in the host. The basic strategy involves inhibiting the mechanisms that play a role in promoting *S. aureus* invasion, pathogenesis, and persistence [51, 54]. Even though, *S.*

aureus is not killed directly by the drug in this strategy, it greatly reduces the ability of bacteria to colonize and infect the host [51].

Several FDA-approved drugs that do not possess direct antimicrobial activity *in vitro* have been shown to inhibit important virulence factors and toxins. For example, salicylic acid, the major metabolite of aspirin, inhibits the global regulators of virulence genes in *S. aureus* such as *sar*A and *agr* [57]. Repression of these two genes, at a clinical achievable dose, leads to the down regulation of various exotoxins and exoenzymes, such as fibronectin protein binding genes (*fnb*A and *fnb*B) and α-hemolysin (*hla*), which are responsible for *S. aureus* adhesion and host tissue cytolysis[57, 58]. This may have the potential to be used as an adjunctive agent for the treatment of multidrug-resistant *S. aureus* infections [57].

3.2. Efflux pump inhibitors

Efflux mediated resistance towards antibiotics in *S. aureus* has been gaining more attention recently and is recognized as the first line of bacterial defense against antimicrobials [59]. Several efflux pumps in staphylococci are associated with resistance to various antimicrobials. Efflux pumps such as Tet(K) and Tet(L) contribute to tetracycline resistance, NorA, NorB, NorC, MepA and MdeA are associated with fluoroquinolone resistance, while Mef(A) and Msr(A) mediate resistance to macrolides [59, 60].

FDA-approved drugs have been shown to inhibit important efflux pumps in *S. aureus.* For example, the phenothiazine group of drugs such as chlorpromazine, fluphenazine, prochlorperazine, and thioridazine, which are primarily used for the treatment of schizophrenia and other psychotic disorders, showed marked inhibitory activity against efflux pumps in *S. aureus* [61, 62]. All four drugs have also been found to inhibit NorA-mediated efflux in *S. aureus* and enhance the activity of norfloxacin several fold [63]. Chlorpromazine and thioridazine have also been shown to reduce MRSA resistance to oxacillin [64]. Similarly, reserpine, an antipsychotic and antihypertensive drug, also inhibits an efflux pump in *S. aureus* that subsequently makes it susceptible to both oxacillin and norfloxacin [63, 64]. Another antihypertensive drug, verampil, has also been shown to reduce fluoroquinolone-resistance in *S. aureus* [65, 66].

Proton pump inhibitors, such as omeprazole and lansoprazole, which are used for the treatment of gastroesophageal efflux and dyspepsia in humans, have also been proven to be potent inhibitors of *S. aureus* efflux pumps [67]. These drugs greatly enhance the activity of fluoroquinolones such as levofloxacin, ciprofloxacin, and norfloxacin in strains of *S. aureus* expressing NorA [67]. Therefore, therapeutic development of bacterial efflux pump inhibitors (in combination with antimicrobials to permit entry of the antimicrobial into the pathogen) is a useful strategy to consider as a treatment for *S. aureus* infections. However, a limitation of the non-antibiotic drugs discussed above is none of these drugs possess activity at a concentration lower than those achievable in human serum [67]. Hence, future studies are needed to focus on making modifications to these drugs to enhance their activity against *S. aureus*. Additionally, subtractive genome analysis and bioinformatics in silico can be used to screen FDA-approved drug libraries to identify more potent efflux pump inhibitors within the applicable clinical range in humans [68, 69].

3.3. Immuno-modulatory drugs

S. aureus possesses diverse immune evading mechanisms to alter the host immune response in such a way that favors their invasion, survival, and replication in the host [70, 71]. Hence, modulation of this complex host immune response to the pathogen is another reasonable approach to target these bacterial infections that has been widely investigated in recent years [52, 55]. In general, pathogens develop strategies to become invisible to the host immune system and in turn the host fails to mount an effective immune response to clear the pathogen [70-72]. On the other hand, there are circumstances where pathogens, such as *S. aureus* and its virulence factors, are capable of hyper stimulating the host immune system, leading to the uncontrolled production of inflammatory markers and other mediators which result in tissue damage and septic shock [73, 74]. This happens more often in acute infections such as in sepsis where the strong inflammatory response and cytokine storm that follows may lead to shock and death [75-77]. In addition, *S. aureus* is also known to secrete various exotoxins such as α-hemolysin, toxic shock syndrome toxin (TSST-1) and leukocidins which can activate antigen-presenting cells (APCs) and T-cells leading to the induction of a strong inflammatory cascade reaction [73, 74, 78]. Superantigens such as TSST-1 and enterotoxins also bypass normal antigen processing by APCs and induce direct proliferation of T-cells, even at a picomolar concentration [78, 79]. Hence, finding immunomodulatory agents that can be effectively combined with antibiotics may produce a better outcome in patients afflicted with a *S. aureus* infection. [80-83].

Non-antibiotic FDA-approved drugs with immuno-modulatory activity to treat bacterial infections have been investigated by various researchers. Even though some of these drugs have no direct antimicrobial activity *in vitro*, they have been shown to aid in achieving a better resolution of staphylococcal infections by reducing toxin production or by modulating host immune response to enhance bacterial clearance.

3.3.1. Statins—Statins are one of the major classes of FDA-approved lipid lowering drugs that act on HMG-CoA reductase; these drugs have been widely used to prevent cardiovascular disease in humans [84-86]. In addition to their role in cardiovascular disease, numerous functions of statins, independent of their lipid lowering property, have been studied recently [87]. The antibacterial activity of statins, particularly simvastatin, has been explored by several groups [88-95]. However, the high MIC value obtained for statins is a major concern with using statins directly as antimicrobial agents [96]; this has led to researchers searching for alternative uses for statins for treating bacterial infections.

Statins act at various cellular and molecular levels and regulate multiple anti-inflammatory actions, reduce oxidative stress, and inhibit leukocyte-endothelial interactions and leukocyte migration. All these effect are beneficial in treating sepsis [97]. Furthermore, statins inhibit several different cytokines including TNF-α, IL-1β, IL-6, and IL-8, thereby lowering the inflammatory activity of neutrophils and macrophages and dampening the immune response involved in sepsis [97-103]. In addition to the extensive inflammatory response, the release of several mediators such as C-reactive protein also plays a major role in sepsis [104]. C-reactive protein promotes thrombus formation by enhancing endothelial cell–monocyte interaction, increases tissue factor expression, and activates the complement

system leading ultimately to organ dysfunction and death [97, 104, 105]. However, statins greatly reduce the levels of C-reactive protein and its subsequent actions in sepsis [106-108]. Statins also inhibit leukocyte migration by reducing various adhesion molecules such as VLA4, P-selectin, CD11b, CD11a and CD18 [109-111]. In addition, a study demonstrated that simvastatin pre-treatment also reduces *S. aureus* α-toxin induced leukocyte rolling, adhesion, and transmigration [112]. Furthermore, the overall beneficial role of statins in *S. aureus* septicemia is supported by a retrospective and clinical study which demonstrated significant reduction in mortality among patients with statin therapy compared with patients not taking statins [96, 113, 114]. Hence, the promising evidence compiled thus far of statins in limiting the effects of sepsis make it worthwhile to investigate the exact molecular mechanism by which statins exhibit their action to propel them into clinical trials in the future, as a novel therapeutic approach for sepsis management.

3.3.2. Nicotinamide—Beyond the use of nicotinamide (vitamin B3) as a supplement, it inhibits inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α and is used for the treatment of inflammatory skin disorders such as atopic dermatitis and acne vulgaris [115, 116]. In addition, nicotinamide, in combination with nafcillin, improved the survival outcome of staphylococcal septic shock in mice [117]. However, the exact molecular mechanism behind this immune modulation activity remains unclear. Another study showed nicotinamide enhanced *S. aureus* killing *in vivo* by modulating host factors [118]. Host factors, such as phagocytic ability of monocytes and macrophages, greatly influence bacterial clearance. In particular, a higher expression of anti-staphylococcal peptides such as lactoferrin (LTF) and cathelicidin in monocytes and macrophages greatly increases their phagocytic ability and bacterial killing [118-121]. However, the expression of antimicrobial peptides (LTF and cathelicidin) in phagocytic cells is regulated by CCAAT/enhancer-binding protein ε (C/EBPε), a myeloid-specific transcription factor [118-121]. Nicotinamide increases the activity of C/EBPε in neutrophils and enhances the killing of *S. aureus* up to 1000-fold *in vivo* [118]. Hence, by manipulating C/EBPε expression, the phagocytic ability of certain immune cells can be enhanced, which further increases their bactericidal activity. [118].

Additionally, nicotinamide also reduces staphylococcal enterotoxin (SEB)-induced responses [122]. Nicotinamide inhibits the SEB-induced T-cell proliferation and inflammatory cytokines such as IL-2 and IFN-γ, and protects mice from SEB-induced toxicity [122]. Thus, taken collectively, nicotinamide with potent immunomodulatory activities via increased *S. aureus* killing and damping the SEB-induced inflammatory response should have therapeutic value for the treatment of staphylococcal infections.

3.3.3. Dexamethasone—Dexamethasone is a steroid drug with potent anti-inflammatory and immunosuppressive activity that has been used for the treatment of various systemic and localized skin diseases. Being a potent anti-inflammatory drug, it also inhibits staphylococcal enterotoxin (SEB)-induced inflammatory cytokines such as TNF-α, IFN-γ, IL-1α, IL-2, and IL-6 and protects mice from hypothermia and shock [123-126].

3.3.4. Rapamycin—Rapamycin, a FDA-approved immunosuppressive drug is used to prevent graft rejection in renal transplantation [127]; it has also been shown to have a

protective effect in a SEB-induced septic shock mice model by inhibiting cytokines such as TNF-α, IFN-γ, IL-2, IL-6, and IL-1α. Additionally, it inhibits production of chemokines such as chemo attractant protein 1 (MCP-1) and macrophage inflammatory protein 1(MIP-1) in peripheral blood mononuclear cell PMBC [128, 129]. When tested i*n vivo*, rapamycin protected all treated mice from lethal staphylococcal shock even when administrated 24 hours after SEB challenge [128, 129].

3.3.5. Pentoxifylline—Pentoxifylline, a FDA-approved drug used for the treatment of intermittent claudication resulting from peripheral artery disease, has a protective role on SEB or TSST-1 induced lethal effects [130, 131]. It suppresses T cell activation and inhibits the cytokines TNF-α, IFN-γ, and IL-1α [130]. Furthermore, pentoxifylline prevents mice lethality in a SEB-induced shock model [130].

The examples described above demonstrate the great potential of FDA-approved non-antimicrobial immunomodulators to be combined with traditional antimicrobials to modulate the host immune response and can be further explored as a novel viable therapeutic strategy for the treatment of staphylococcal infections.

3.4. Anti-biofilm agents

Biofilm-forming *S. aureus* often cause serious complications leading to life-threatening infections [132]. Studies on staphylococcal biofilm present on indwelling medical devices such as catheters, implanted devices, and prosthetic heart valves have drawn great interest over the past few decades [132]. *S. aureus* biofilm-associated infections are challenging to treat with conventional antibiotics [132, 133]. Hence, novel drugs and strategies are in immediate need to deal with biofilm infections [133]. Several FDA-approved non-antibiotic drugs have been shown to possess anti-biofilm activity. For example, nitazoxanide (NTZ), an anti-protozoal agent approved for the treatment of *Cryptosporidium parvum* and *Giardia intestinalis* infections in humans, is shown to have anti-biofilm activity [134]. Nitazoxanide exhibits anti-staphylococcal activity at a MIC ranging from 8 to 16 μg/ml. Additionally, at sub inhibitory concentrations (IC_{50} of 1 to 3 μg/mL), NTZ is shown to inhibit biofilm formation by *Staphylococcus epidermidis* [135].

Several FDA-approved drugs are known to disrupt adherent microbial biofilms. Examples include auranofin (anti-rheumatoid drug), benzbromarone (gout drug), pyrvinium pamoate (antihelminthic), yohimbine hydrochloride (mydriatic vasodilator), and zotepine (antipsychotic) which have all been shown to be capable of inhibiting pre-formed microbial biofilms [136]. Further testing of these drugs against different staphylococcal biofilms, both alone and with conventional antimicrobials, should be considered as a new avenues to target multidrug-resistant staphylococcal infections and associated biofilms.

4. Identifying new antibiotic leads from approved drugs, which can serve as novel antibiotics

From 2008-2012, only three new antibiotics received approval from the FDA [137]. Interestingly, in 2014, thus far the FDA has already approved three new antibiotics

(dalvance, tedizolid phosphate, and oritavancin) indicating the agency is recognizing the urgent need for new antibiotics to treat difficult bacterial infections; all three approved drugs are indicated for use in treating acute bacterial skin and skin structure infections caused by pathogens such as MRSA [138, 139]. These antibiotics are not new drug classes but rather modified derivatives of older antibiotics which interfere with the same biochemical pathways and molecular targets known for many years. For example, dalvance and oritavancin belong to the glycopeptide class of antibiotics (which interfere with bacterial cell wall synthesis) while tedizolid phosphate is an oxazolidinone which inhibits bacterial protein synthesis.

Though numerous new molecular/druggable targets inside bacteria have been identified in recent years, no compounds have been successfully developed (and received approval) that interact and bind to these targets. Given that only four new antibiotic classes have been identified in the past 40 years using the traditional drug discovery approach, new techniques need to be considered to discover drugs capable of binding to these unique targets [140]. Drug repurposing presents a new method to screen for existing drugs that can interact with these critical targets inside pathogens. This could lead to the development of new antimicrobial classes, which interact with different molecular targets compared to traditional antibiotics. Understanding which moiety on the drug interacts with the molecular target can also permit medicinal chemists to make rational modifications to the parent drug to construct analogues with enhanced binding affinity for the target (with the hope of improved antimicrobial activity), improved pharmacokinetic profile of the drug, and reduced toxicity to host tissues. Also this could permit the identification of new bacterial targets which have not been previously known.

5. Challenges for repurposing non-antibiotic drugs for *S. aureus*

Though repurposing approved drugs for use as antimicrobials is an exciting avenue for discovery of new potential treatments for bacterial infections, there are multiple obstacles hindering progress in identifying and developing these agents. One of the biggest challenges in the field of antibiotic drug discovery is the lack of interest by pharmaceutical companies and industry to invest resources in this area. The reality is that the vast majority of drugs currently available in the market were discovered by the pharmaceutical industry. In the United States alone, only 9% of new drugs discovered between the years of 1960 and 1969 came from government agencies, universities, and not-for-profit organizations [8]. This trend continued to hold true in latter parts of the 20th century as over 93% of new drugs approved in the United States, from 1990 to 1992, were procured from industry; government agencies and academic institutions each accounted for just over 3% of new drugs in this time span [10]. Thus industry is a key cog in the identification and development of drugs which are capable of reaching the healthcare setting. However, given the low return on investment for antibiotics, companies, particularly Big Pharma, have moved away from developing new antibiotics. This can be illustrated with a simple example; from 2009-2012, Merck's leading medication for diabetes (Januvia) outsold its top-selling antibiotic (Invanz, a carbapenem antibiotic) by US$11 billion [141]. Moreover, a review of the top 100 best-selling drugs from April 2013 through March 2014 revealed treatments for chronic diseases such as rheumatoid arthritis depression, asthma, high-cholesterol, multiple sclerosis, Alzheimer's

disease, diabetes, AIDS, high blood pressure, and cancer generated the most sales for pharmaceutical companies; interestingly no antimicrobials were found on this list. Given the associated costs involved with drug discovery, the lack of sales generated by antibiotics (in comparison to drugs developed for chronic diseases such as asthma, diabetes, and high blood pressure), and stringent regulations required for new antibiotics to receive regulatory approval, this significantly reduces the incentive needed by companies to pursue developing novel antimicrobials [137]. This has led to several major companies, including Pfizer and Roche, to terminate their antibiotics research & development division; as of 2013, only four major pharmaceutical companies have active antimicrobial drug discovery programs [140, 141]. This leaves government agencies, academic institutions, and small companies with the burden of filling this gap to generate new antimicrobials. While repurposing existing drugs is a mechanism for these institutions to curb costs associated with the drug discovery process, most of these agencies lack the resources available to industry for drug discovery. Additionally, these organizations face a second major obstacle in the path to repurposing drugs as antimicrobials.

A second major challenge to repurposing approved drugs as antimicrobials pertains to the lack of accessibility to libraries containing clinical drug collections. As highlighted by Chong and Sullivan, no single collection of the nearly 10,000 known clinical drugs currently exists [7]. Instead these drugs are dispersed throughout several different collections or are not available to researchers (in part due to existing patents present for certain drugs). Among the publicly available compound collections include the National Institute of Neurological Disorders and Stroke (NINDS) collection of 1,040 compounds, the Prestwick Chemical Library in Washington, DC (containing more than 1,000 approved drugs), and the Johns Hopkins Clinical Compound Library (consisting of more than 1,500 compounds) [7]. Combined with other drug collections available for commercial purchase, this amounts to only 40% of the total known approved drugs and clinical molecules which are available for screening for antimicrobial activity [7]. However, redundancy and overlap between these different libraries presents an additional problem as a compound may be present in more than one collection making screening these compounds more difficult.

Obtaining access to the remaining 60% of clinical drugs, for screening for antimicrobial activity, is a significant impediment to identifying new clinical applications for these drugs. Moreover, it would be valuable to researchers if they can gain access to libraries of compound metabolites and drugs, which entered phase II and III clinical trials but failed to receive approval for the initial clinical indication. Most drugs fail in phase II clinical trials because they prove ineffective in treating the disease they were initially intended to be used for [11]. Though these compounds may not have succeeded in gaining approval for their initial clinical application, they may still have promise for alternative uses, for example as antibiotics for *S. aureus* infections. Gaining access to these compounds, clinical data generated for these compounds, and information pertaining to why they failed in clinical trials will permit researchers to rationally design potential solutions to overcome these issues in repurposing these compounds for other clinical applications. However, many of these clinical failures are often not made publicly accessible by pharmaceutical companies (for competitive and financial reasons); additionally given these companies often are focused on developing drugs for specific diseases, they may not have the resources (i.e. models to

study infectious diseases in humans) or personnel to identify new applications for these failed compounds [11]. Establishing relationships and bridging the gap between industry (who would provide these compounds and clinical data garnered), academic research institutions (to screen these compound libraries for hits for antimicrobial activity), and government agencies (to assist with sponsoring clinical trials to test drugs to be repurposed as antimicrobials) is very important in order to find new applications for both approved drugs and compounds which have entered into late stage clinical trials but ultimately failed.

6. CONCLUSION

Development of new antimicrobials is very slow and there are not enough new antimicrobials in the drug pipeline to keep pace with the emergence of multidrug-resistant bacterial strains. Moreover, pharmaceutical companies lacking interest in antimicrobial drug discovery has contributed to the dearth of new and novel antibiotics. Therefore alternative strategies are in urgent need to battle against multidrug-resistant infections such as those caused by *S. aureus*. Repurposing approved drugs presents an emerging approach with reduced cost, discovery time, and risk associated with antibiotic development. We presented several approved drugs that possess potent anti-staphylococcal activity *in vitro*; with further mechanistic and *in vivo* studies, these drugs might be a potential candidate drugs that can be considered for systemic and (or) topical applications. Independent of antimicrobial activity, some drugs also have the ability to interfere with *S. aureus* pathogenesis and modulate host immune response to enhance bacterial killing and clearance. This is an additional novel application of the approved drugs which warrants further exploration. With the promising activity and the past success in drug repurposing, repositioning existing drugs might form a potential alternative strategy to discover new antimicrobials and might drive interest of researchers both in academia and the pharmaceutical industry to invest more research resources in this area.

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Table 1:

List of drugs, which have been repurposed as anti-infective agent.

Drugs	Initial use	Repurposed use	References
Auranofin	Antirheumatic agent	Amoebiosis	[16]
Miltefosine	Skin metastases (breast cancer)	Vischeral leishmaniasis	[142, 143]
Amphotericin B	Antifungal	Visceral leishmaniasis	[144]
Dapsone	Pulmonary tuberculosis	Malaria and Leprosy	[145-148]
Eflornithine	Antitumour agent/*P. carinii* infection in AIDS patients	Human African sleeping sickness	[149-153]
Doxycycline	Antibacterial	Malaria	[154]
Paromomycin	Antibiotic	Visceral and cutaneous leishmaniasis	[155-157]
Spiramycin	Antibacterial	Toxoplasmosis	[158]
Chloroquine	Malaria	Amebiasis and sarcoidosis	[159, 160]
Atovaquone	Malaria	Toxoplasmosis and *P. carinii* pneumonia	[161-163]
Pyrimethamine	Malaria	Toxoplasmosis	[161, 164-166]

Table 2:

Approved drugs with activity against *S. aureus*

Drugs	Class/type	MICs against *S. aureus* (μg/ml)	References
5-fluoro-2'-deoxyuridine	antineoplastic	0.0007-0.002 *	[35]
Auranofin	anti-rheumatoid	0.125-0.5 *	[18, 19]
Ebselen	organoselenium compound	0.2 *	[28]
5-fluorouracil	antineoplastic	0.5 – 0.8	[33]
Mitomycin-C	antineoplastic	0.25	[167]
Mithramycin	antineoplastic	0.25	[167]
Disulfiram	alcohol deterrent	1.33	[168]
Trifluprομazine	antipsychotic	2-5	[169]
Dactinomycin	antineoplastic	4	[167]
Oxymetazoline	Vasoconstrictor(decongestant)	5	[170]
Daunorubicin	antineoplastic	8	[167]
Doxorubicin	antineoplastic	16	[167]
Levocabastine	antihistamines	20	[170]
Emadastine	antihistamines	20	[170]
Dicyclomine	antispasmodic	25	[171]
Prochlorperazine	antipsychotic	20-25	[172]
Simvastatin	antihyperlipidemic	29-74	[173]
Celecoxib	NSAIDs	32	[174]
Tetrahydrozoline	vasoconstrictor (decongestant)	50	[175]
Methotrexate	antineoplastic	64 – 102	[33]
Tegaserol	narcotic and analgesic	80	[170]
Amitriptyline hydrochloride	antidepressant	100	[176]
Azelastine hydrochloride	antihistaminic	125- 250	[177]
Mitpranolol	antiarrhythmic, antiglucoma	140	[178]
Promethazine	neuroleptic and antihistaminic	125- 250	[177]
Butorphanole	narcotic and analgesic	180	[178]
Diclofenac	anti-inflammatory	200	[179]
Tropicamide	anticholinergic	200	[178]
Oxyfedrine	vasodilator	200-250	[180]
Aminopterin	antineoplastic	256	[167]
Fluvastatin	antihyperlipidemic	400	[170]
Ticlopidine	anticoagulant	450	[170]
Ketamine	anesthetic	450	[170]
Proxymetacaine	anesthetic	500	[170]
Mequitazine	Antihistaminic and anticholinergic	625-125	[177]

Drugs	Class/type	MICs against *S. aureus* (μg/ml)	References
Cyproheptadine hydrochloride	antihistaminic	625-125	[177]
Ibuprofen	NSAIDs	1250	[181]
Acetaminophen	NSAIDs	1250	[181]
Telmisartan	antihypertensive	2000	[170]
Perazine	antipsychotic	2000	[182]
Amlodipine	antihypertensive	3000	[175]
Docusate sodium	laxative	3000	[183]
Etodalac	NSAIDs	4000	[170]
Alverine	spasmolytic	4000	[170]
Fluvoxamine	thymoleptic	4000	[182]
Tolfenamic acid	NSAIDs	5000	[170]
Temozolomide	antineoplastic	5000	[170]
Acepromazine	antiemetic, sedative	5000	[175]
Riluzole	anticonvulsive, antiepileptic	5000	[182]
Tamoxifen	anti-neoplastic	6000	[182]
Solifenacin succinate	spasmolytic	7000	[183]
Perphenazine	antipsychotic	8000	[175]
Oxaprozin	NSAIDs	13000	[170]
Citalopram	antidepressant	13000	[183]
Zofenopril	ACE inhibitor	15000	[182]
Sertraline	antidepressant	16000	[184]
Chlorpromazine	antipsychotic	20000	[175]
Acebutolol	antihypertensive	23000	[175]
Clopidogrel	anticoagulant	24000	[183]

* MICs below the plasma concentration of the drug in humans