Editorial

ANNALS OF MEDICINE & SURGERY

OPEN

Binding to the immutable targets: a novel strategy to combat surgical-site infections caused by multidrug-resistant superbugs

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Antimicrobial resistance is an emerging issue that has come up as a matter of concern for scientists and the search for novel antibiotics is gaining pace day by day. In a recent 2023 study, researchers have come up with a novel antibiotic, clovibactin produced by uncultured soil bacteria that can kill bacteria through binding immutable targets thereby evading resistance[1]. This finding not only has grabbed attention, but also has ignited interest in developing antibiotics that target evolutionarily conserved and immutable targets of bacterial pathogens especially those turned into multi-drug-resistant ones. One such condition that highly demands the intervention of such novel antibiotics is surgical-site infections (SSIs). SSI is a condition arising due to the presence of pathogenic microorganisms in a surgical site or any organ or cavity. SSI is the third most prevalent nosocomial infection worldwide, found in 15% of post-surgical patients with infections[2]. SSIs lead to clinical and economic burdens for patients and include an increased risk of readmission. Majorly, SSIs develop after operation through the pathogens thriving in the hospital environment itself or are endogenous in origin[3]. The report of the European Centre for Disease Control and Prevention in 2013 revealed the prevalence of various hospital-associated infections to be as high as 3.4%[4]. Although such instances have reduced in the past decade, there has been an alarming shift towards drug-resistant pathogens, leading to worse prognoses and increased costs of treatment[2].

The emergence of multi-drug-resistant (MDR) pathogen-associated SSIs and the challenges

Antimicrobial resistance to pathogens is an alarming issue and an emerging threat to patient health. The major risk factors leading to antibiotic resistance include prior antibiotic administrations and previous infections[5]. Among the various bacterial strains causing SSIs, *Staphylococcus aureus* and *Escherichia coli* are the widespread ones with resistance ranging from 42.7 to 44.7% and from 13.3 to 15.3%, respectively[6]. Similarly, vancomycin-resistant Enterococci, MDR Enterococci and methicillin-resistant *Staphylococcus aureus* remain other major concerns[7]. There has also been a large enhancement in SSIs due to gentamicin-resistant Enterococci that are transmitted through proximity with medical staff. In several cases, these infections are endogenous involving surgeries of the urinary or gastrointestinal tract, and oral cavity[8].

With the increase in the incidences of multidrug resistant Enterococcus infections in SSI patients, there has been a major problem of lack of therapeutic options. MDR Enterococci have developed a unique range of mechanisms and genetic plasticity, which has allowed them to flourish in the medical setup. These pathogens have high resilience and as a result, can thrive in extreme conditions and have almost developed resistance to all the major antibiotic groups[5]. The site of resistance development is at the level of the cell wall and at times ribosome. The strategies involve decreased affinity for penicillin-binding proteins, drug inactivation, cell signalling target alteration and a decrease in drug uptake[8]. Enterococci can escape β-lactam antibiotics and glycopeptides like vancomycin and teicoplanin both of which halt peptidoglycan synthesis[9]. *Staphylococcus aureus* is another SSI-causing pathogen in which MDR has emerged to a great extent. *Staphylococcus aureus* remains a dreadful human pathogen that can cause stern systemic infections and becomes even more notorious as a multidrug-resistant bacterium. Healthcare professionals are shifting towards vancomycin, to treat methicillin-resistant *S. aureus*. However, uncontrolled use of vancomycin is leading to the development of resistance among *S. aureus* strains[6]. In this scenario, antibiotic development strategies must be modified. The root cause of resistance development is that traditional antibiotics chase common targets leading to evolutionary pressure on pathogens to modify the same. Immutable motifs in this

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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Annals of Medicine & Surgery (2024) 86:28–31

Received 18 September 2023; Accepted 21 November 2023

Published online 4 December 2023

http://dx.doi.org/10.1097/MS9.0000000000001570

regard as antibiotic targets can hinder resistance development and make SSI treatment easier.

Targeting the immutable targets for antibiotic development

With the emerging incidences of MDR-associated SSIs, scientists are being compelled to rethink on target selection of antibiotics. New-generation antibiotics must target essential components, leading to the killing of drug-resistant pathogens (Fig. 1). Recently, in a promising report, a new antibiotic called clovibactin has been discovered from uncultured soil bacteria[1]. This antibiotic unusually kills methicillin-resistant *S. aureus*, daptomycin and vancomycin-intermediate-resistant *S. aureus*, and vancomycin-resistant Enterococci, making it tough for it to develop further resistance. This is because it binds with the immutable part of its targets making bacteria find it hard to evade[1]. Clovibactin acts by targeting the pyrophosphate of multiple indispensable peptidoglycan precursors. This antibiotic tightly winds around pyrophosphate but bypasses the variable elements of precursors, hindering resistance. This potent antibiotic shows much prospect as a novel agent that can kill bacterial pathogens without the risk of resistance development and can open new horizons for the drug development sector specifically for SSIs associated with MDR pathogens[10].

In a 2023 study, new strategies to develop antibiotics against immutable targets of multidrug resistant *S. aureus* have also been highlighted like targeting lipoteichoic acid, filamentous temperature-sensitive protein Z and FabI inhibiting bacterial fatty acid biosynthesis[6]. Moreover, engineered antimicrobial peptides PLG0206, OP-145, and LTX-109 are being developed to target immutable motifs leading to breakage of resistance[6]. Another method that has come up as a strong strategy is to target two-component systems of bacterial signalling. Such a two-component system comprises a sensory histidine kinase and a response regulator. These systems control various virulence and antibiotic-resistance mechanisms. Compounds like diarylthiazole, xanthoangelol B have been proven to be effective histidine kinase inhibitors against multidrug-resistant pathogens[11]. Whereas, compounds like MciZ, CRAMP as FtsZ inhibitors act as successful multidrug-resistant pathogen inhibitors through blocking its assembly[12,13]. Huge success was achieved with controlling methicillin-resistant *S. aureus* when triclosan-derived FabI inhibitors were developed targeting conserved targets and lead to active research to be conducted on promising triclosan analogues[14]. Moreover, if virulence mechanisms are targeted, that may reduce the evolutionary pressure for acquired resistance[15]. Figure 2 represents the precise mechanism of action upon the major immutable targets of multidrug-resistant pathogen. Looking into the prevalence of SSIs caused by MDR pathogens, if similar approaches can be developed for SSIs, especially bacteria with MDR, targeting immutable targets, the problem can be solved to a great extent. Nevertheless, further progress for the clinical translation from bench-side research into bedside reality is necessary.

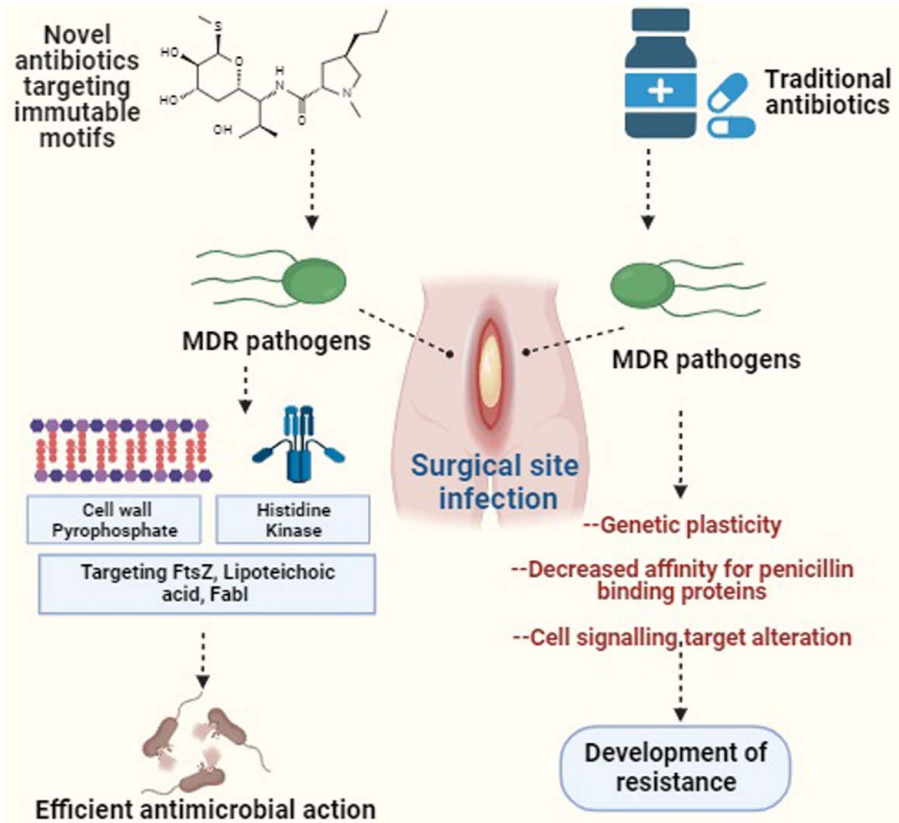

Figure 1. Novel antibiotic development strategies targeting immutable targets like cell wall pyrophosphate, histidine kinase, filamentous temperature-sensitive protein Z, lipoteichoic acid, and fatty acid biosynthesis enoyl-acyl carrier protein reductase-I to overcome problems of surgical-site infections due to multidrug-resistant (MDR) pathogens.

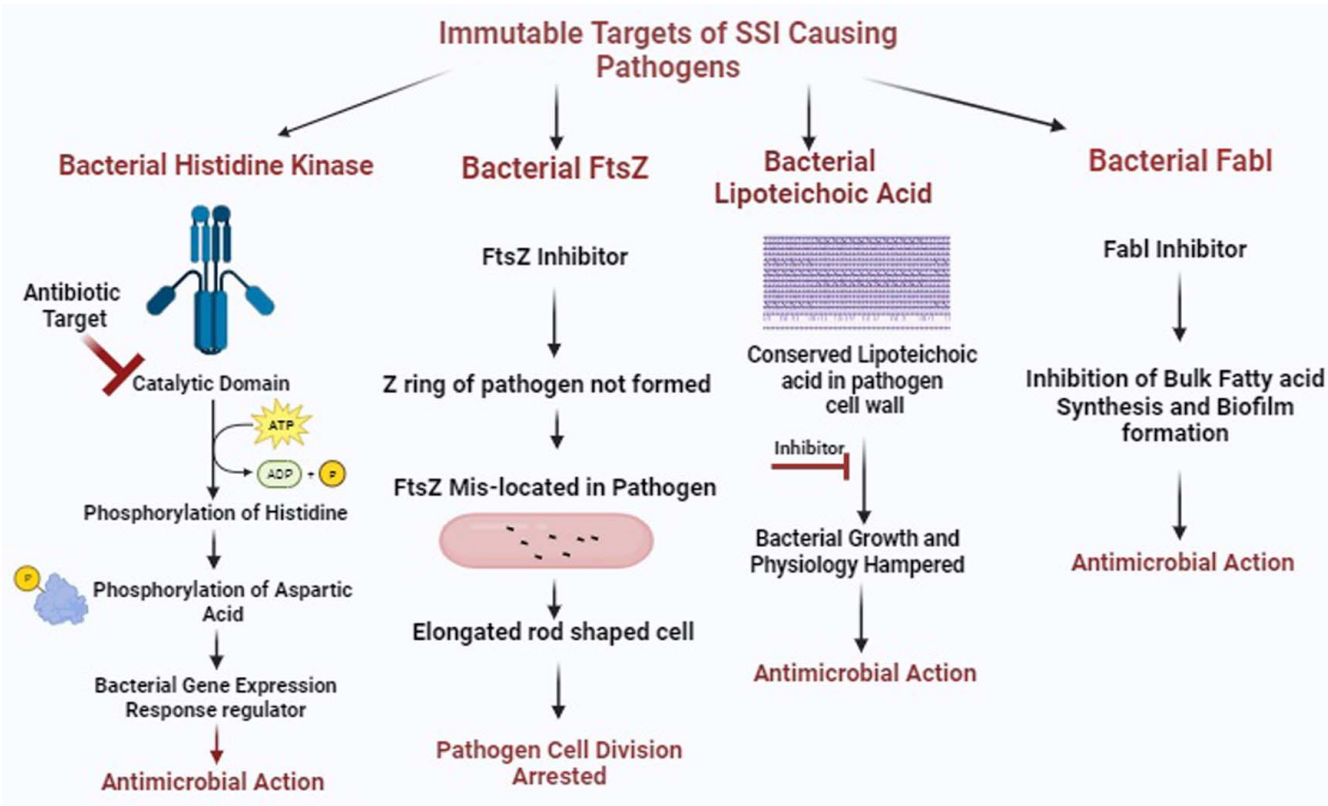

Figure 2. Precise mechanism of action of various antibiotics that target some immutable targets of multidrug resistant pathogen. SSI, surgical-site infection.

Ethical approval

Ethics approval was not required for this editorial.

Consent

Informed consent was not required for this editorial.

Source of funding

No funding

Author contribution

A.S.M.S.: conceptualization, data curation, writing—original draft preparation, writing- reviewing and editing, A.S.: data curation, writing—original draft preparation, writing—reviewing and editing. A.V.S. and S.K.: data curation, writing—original draft preparation, writing—reviewing and editing. R.A.: writing—reviewing and editing, visualization. T.B.E.: writing—reviewing and editing, visualization, supervision

Conflicts of interest disclosure

All authors report no conflicts of interest relevant to this Editorial.

Research registration unique identifying number (UIN)

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

Guarantor

Talha Bin Emran.

Data availability statement

Not required for this editorial.

Provenance and peer review

Not commissioned, externally peer-reviewed

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