

# HOSPITAL ACQUIRED INFECTIONS

The Conundrums Of IV To Oral Switch



VENUS REMEDIES LIMITED



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## *Antimicrobial Resistance*

# INTRODUCTION

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Antimicrobial resistance (AMR) has emerged as one of the principal public health problems of the 21st century that threatens the effective prevention and treatment of an ever-increasing range of infections caused by bacteria, parasites, viruses and fungi which are no longer susceptible to the common antimicrobials used to treat them. Antibiotic resistance in particular is of major concern. “Global crisis”, “return to medical dark ages”, “antibiotic apocalypse” are some of the phrases being used by prominent scientists, physicians, and world leaders to emphasise the catastrophic impact that antibiotic resistance will have on human health and the global economy. In 2014, Lord Jim O’Neill published a review commissioned by the United Kingdom government, entitled “Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations” (the AMR Review) [1]. The review estimated that if left unchecked, by 2050, AMR could result in over 10 million deaths annually and over \$100 trillion of lost global output! To put this into perspective, this damage would be similar to, and likely worse than that caused by the great economic and financial recessions of modern history [2].

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*“We now know that unless addressed swiftly and seriously and on a sustained basis—the growing global problem of antibiotic resistance will be disastrous for human and animal health, food production and global economies.”*

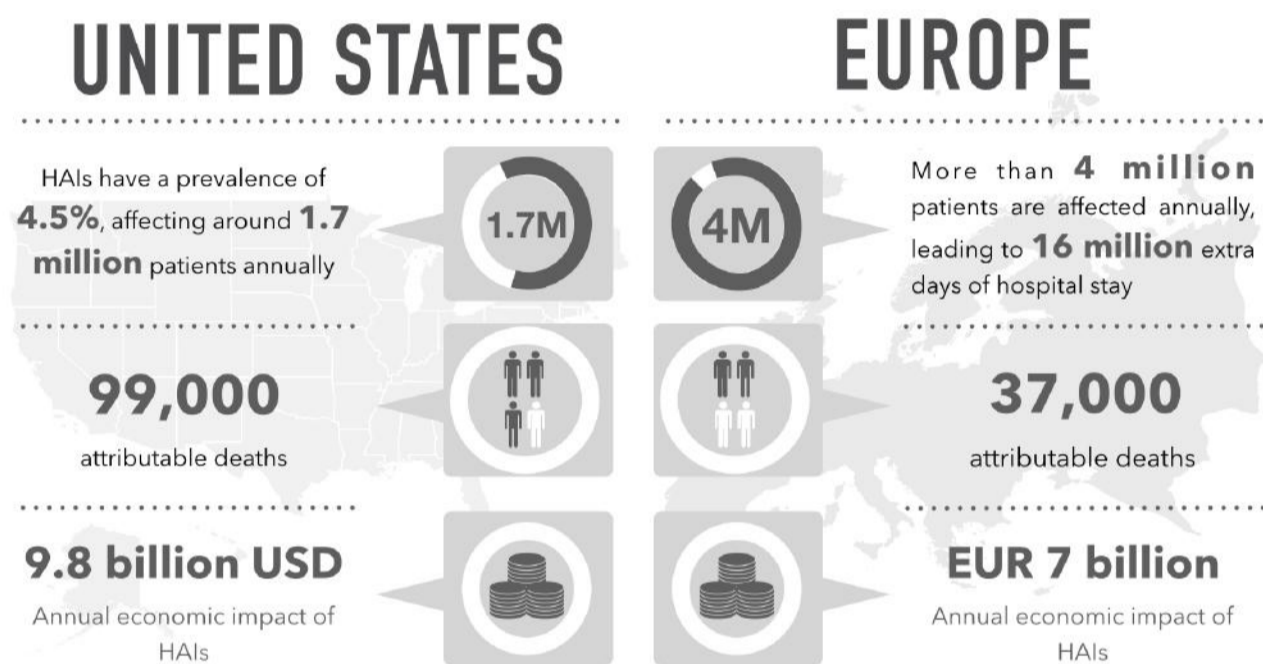
*- Margaret Chan, Ex-Director General of the WHO*

# HOSPITAL ACQUIRED INFECTIONS

AMR unequivocally impacts all healthcare facilities and patients and healthcare providers deal with it on a daily basis in the form of Hospital Acquired Infections (HAIs). A HAI, also referred to as “nosocomial” infection, is an infection occurring in a patient during the process of care in a health-care facility which was not present or incubating at the time of admission. Usually, an infection is considered a HAI if it first appears 48 hours post hospital admission, within 3 days of discharge or within 30 days of an operation [22]. The most common HAIs include pneumonia, surgical site infections, *Clostridium difficile* infection,

blood stream infections, catheter-associated urinary tract infections, etc. The intensive and prolonged use of antibiotics in the hospitals are among the main contributors to the emergence and spread of highly antibiotic-resistant hospital-acquired infections, however, other

factors like presence of highly susceptible immunosuppressed patients and fragile elderly patients, lack of proper hygiene, invasive surgical procedures and intensity of clinical therapy, length of stay in hospital, failure to control spread of infections from patient to patient etc. play an important role [3]. HAI's are frequently associated with difficult to treat pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase (ESBL)-producing gram-negative bacteria including multi-drug resistant (MDR) *Acinetobacter spp.*, *Pseudomonas spp.*, Enterobacteriaceae, among others.



## ACCORDING TO THE WORLD HEALTH ORGANISATION

At any given time over 1.4 million people across the globe suffer from a Hospital-Acquired Infection [21]. On average, 7% of hospitalised patients in developed and 10% in developing countries acquire at least one HAI during hospital stay [4]. This situation becomes more grim when you consider the high mortality rate of 10% that is associated with such infections.

Figure 1: Statistics on hospital-acquired infections in the US and Europe, data from ref. [5, 23]

As can be expected, the situation is worse in developing countries as additional factors such as poor hygiene and sanitation, lack of basic equipment, inadequate infrastructure, overcrowding and pervasive malnutrition and disease proliferate the risk of infection. Resultantly, the incidence of infection in developing countries is expected to be at least twice as that of the US. Faced with this reality, the need for action to turn the tide on this emerging global crisis in healthcare is of vital importance. Antibiotics are an essential pillar of modern medicine and have protected humanity for 75 years against bacterial pathogens but today we once again find ourselves vulnerable and left to the mercy of resistant bacteria.

## IV TO ORAL CONVERSION

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Controlling HAIs require multi-disciplinary efforts like ensuring proper hygiene, implementing strict antimicrobial stewardship, ensuring minimal duration of hospital stay for patients, and warrants a high level of commitment from both healthcare practitioners and hospital administrations.

One effective way is conversion from intravenous (IV) to oral (PO) therapy. This conversion will lead to early discharge of inpatients and avoid the need for hospitalization of outpatients with less severe infections, thereby reducing the exposure of nosocomial pathogens and risk of complications. Three types of IV to PO conversion therapies have been proposed in the literature, namely [6]:

- 1. SEQUENTIAL THERAPY:** It refers to the act of replacing a parenteral version of a medication with an oral counterpart of the same compound. For instance, Conversion of inj. ciprofloxacin 200 mg q12h to tab. ciprofloxacin 500 mg q12h
- 2. SWITCH THERAPY:** It describes the conversion of an IV medication to a PO equivalent; within the same class and has the same level of potency, but of a different compound. For example, switch over from inj. ceftriaxone 1 g BD to tab. cefixime 200 mg BD
- 3. STEP-DOWN THERAPY:** It refers to the conversion from an injectable medication to an oral agent in another class or to a different medication within the same class where

the frequency, dose, and the spectrum of activity (in the case of antibiotics) may not be exactly the same. For example, conversion of inj. cefotaxime 1 g to tab. ciprofloxacin 500 mg

The ideal route of administration of any medication is the one that achieves serum concentrations sufficient to produce the desired therapeutic effect [6]. The major difference between IV and oral therapy is *bioavailability* and the onset of action. *Bioavailability* is a measure of the amount of an administered dose that reaches the bloodstream. While all IV medications have a bioavailability of 100%, this is not the case with oral medications and only a few antimicrobial drugs have a high oral bioavailability. These include Ciprofloxacin, Doxycycline, Levofloxacin, Linezolid, Metronidazole, Minocycline, Ampicillin, Azithromycin, co-amoxiclav, TMP + SMX, etc.. Nonetheless, these constitute less than 10% of the total IV antibiotic arsenal. Reason being, a large number of antibiotics fall under BCS (Biopharmaceutics Classification System) class III/IV and are characterized by low permeability and/or solubility when given orally. These drugs exhibit zero or poor oral bioavailability and thus are mainly administered intravenously.

The current standard-of-care drugs to treat serious infections caused by gram-negative bacteria include beta-lactams (BLs), like Meropenem, Imipenem, Doripenem, or BL- beta-lactamase inhibitor (BLI) combinations, like Piperacillin-Tazobactam, Ceftolozane-Tazobactam, Meropenem-Vaborbactam, Ceftazidime-Avibactam, etc. [7-11], that contain one or more components with a poor oral bioavailability. This is the main reason that precludes the effective conversion from IV to Oral in clinical settings as most of the available oral antibiotics, especially ones used to treat gram-negative bacteria, have limited or no activity against the MDR pathogens that are increasingly found in the hospital flora.

To enable effective conversion, oral antibiotics must achieve serum concentrations comparable to that of its IV counterpart. Generally, due to the lack of effective oral options for sequential and/or switch-over therapy conversion for treating life-threatening infections, clinicians are left with the less efficacious step-down therapy to a lower grade antibiotic increasing the likelihood of treatment failure or relapse. As a result, clinicians tend to opt for IV medications at the time of admission and continue them till patient

discharge, leading to a longer hospital admission duration and increased chance of contracting a HAI.

Ideally, a sequential or switch therapy, if available, will aid in managing the menace of nosocomial pathogens. Conversion from IV to oral administration is one of the major recommendations made in the antimicrobial stewardship guidelines by the Infectious Diseases Society of America (IDSA) [15]. Other advantages from conversions of intravenous (IV) to oral therapy include - earlier discharge with increased comfort and easier mobilisation of patients; shorter length of hospital stay and better use of hospital beds; reduction in both direct and indirect costs (Direct - medication, lodging and Indirect - diluents, equipment, needles); an associated reduction in workload without sacrificing patient safety; decrease in device associated infections; decreased risk of IV line associated complications like thrombophlebitis; saves medical and nursing time [6].

A Vancouver General Hospital study showed that the conversion from intravenous to oral administration of ciprofloxacin by pharmacists led to a 23% reduction in unnecessary prescription of intravenous medications and subsequently, healthcare costs [16]. Furthermore, a Taiwan study on the clinical and economic impact of conversion from intravenous to oral administration of levofloxacin resulted in a reduction of 11.1 days in the mean length of hospitalization and 40% reduction in the total cost of hospitalization after the intervention [17]. Similar advantages of conversion from intravenous to the oral antimicrobial administration have been reported in various studies worldwide. Like many good ideas, conversion therapy looks, with the benefit of hindsight, an obvious concept.

It is also worth adding that the clinical trial guidelines that are adopted for testing new antibiotics often require IV to Oral conversion [24]. However, due to poor bioavailability of the investigative compounds in recent trials like TANGO 1 and RECAPTURE [18-19], sponsors had to opt for a step-down therapy to a lower class of antibiotic. Not only does this lead to a decline in patient cure rates from End-of-IV therapy (EOIVT) to the end of treatment (EOT) (and subsequently to the test-of-care visit) as seen in the studies, it also confounds the true efficacy of the investigative compound. Furthermore, if there were an Oral version of these drugs, its efficacy could potentially be proven during the same development program, saving millions of dollars of additional development costs. The poor return-on-investment (ROI) associated with antibiotic drug development is a serious

concern and has been driving more and more companies out of antibiotic drug development. We believe that if both the IV and Oral versions of a drug were to be developed concomitantly, not only will it significantly improve the ROI but will also aid in implementing antimicrobial stewardship that would benefit all stakeholders.

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*The Solution Brief*

# STEALTH TARGETED NANOPARTICLES

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With an aim to preserve the life of existing antibiotics and to guide better clinical decisions, Venus Medicine Research Centre, research wing of Venus Remedies Limited, have developed a unique platform called Stealth Targeted Nanoparticles (STN). STN is a novel concept of stealth-targeted nano medicine. It employs a polymeric backbone with stealth properties to bypass macrophagic detection by body's immune system, along with a targeting moiety for delivering the drugs with "zero" or very low oral bioavailability of BCS Class 3/4 like Ceftazidime, Ceftriaxone, Meropenem, Vancomycin, many other BL + BLI combinations through the intestine and achieve serum concentrations sufficient to produce the desired pharmacodynamic effect. This biodegradable and biocompatible platform removes the inherent hurdles of permeability and solubility posed by these drugs.

The platform has been tested on multiple IV drugs like Ceftriaxone, Meropenem and Vancomycin in the early proof-of-concept studies. These were developed as pH-sensitive, stealth-targeted nanoparticles with size range around 20 to 200 nm. In vivo pharmacokinetic studies after oral administration in Albino Wistar rats revealed relative bioavailability of these drugs up to 70 percent compared to IV administration (unpublished data). Caco-2 cell uptake studies in VRP001 (a novel BL+BLI combination with a very poor bioavailability of the main beta-lactam drug) revealed higher uptake of targeting-ligand functionalized nanoparticles in comparison with their plain counterparts and pristine drug solutions. Further studies revealed a spherical shape of nanoparticles

with a smooth surface, exhibiting excellent stability in simulated biological fluids, a high melting point and no chemical molecular interaction. An amorphous molecular level dispersion of the drug in the matrix was observed, allowing increased absorption.

The resultant product from the STN platform is a drug-containing nanoparticle matrix that is easily dissoluble in water and other fluids. This was done to increase therapy compliance among the paediatric and geriatric set of patients that are most susceptible to HAIs. STN delivered antibiotic due to its size, bioavailability and targeting ligand is suspected to have the same blood/tissue concentrations as its IV counterpart, which will also lead to the same therapeutic response. We strongly believe that this platform is a promising tool for oral delivery of poorly bioavailable drugs, especially those for which IV formulations are already available and are widely used.

The rational use of economic resources is as important as the consistent use of clinical resources, and this importance is especially significant for antibiotics, which represent a significant portion of health care expenses [20]. STN has the potential to redefine the economics of antibacterial drug development, improving ROI and incentivising innovators to re-explore anti-infective research. This may in turn help us avoid a post-antibiotic era.

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*To learn more about the STN platform technology, we invite you to join us at:*

*World AMR Congress, Washington D.C.*

*25<sup>th</sup> October, 2018 at 12:35 p.m.*

*“The scale and nature of this economic threat (AMR) could wipe out hard-fought development gains and take us away from our goals of ending extreme poverty and boosting shared prosperity”*

*- Jim Yong Kim, President of the World Bank Group*



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