

Antibiotic Development in an Era of Burgeoning Bacterial Resistance- Therapies for Complicated Skin Infections

Glenn S Tillotson*

***Corresponding Author:** Glenn S Tillotson, Senior Partner, Transcrip Partners LLP, 2941 Honeymead Road, Downingtown, PA 19335 USA; Tell: 001 858 361 3613; E-mail: gtillotsonconsult@yahoo.com

Anti Microbial Resistance (AMR) has become a global health threat and is considered to be driven by antibiotic use. This means not only inappropriate use but also how the drug is taken by the patient and a part of the adherence issue is the complexity of the administrative regimen.

Antibiotics have been in use for about 75 years with skin infections being one of the early target indications. Indeed the early courses of penicillin were given four or more times a day for 10-14 days [1]. This course was not based on good science but rather “best estimates” or clinical perspective. In the intervening period significant changes in the management of skin infections, especially complicated (CSSI) or as in the USA, Acute Bacterial Skin and Skin Structure Infections (ABSSSI) have occurred.

I have chosen complicated skin infections as an example where scientifically based shifts in dosing regimen have contributed to improvements in adherence and potentially healthcare savings without loss of clinical efficacy. Another reason for focusing on CSSI is the remarkable increase in Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections causing skin infections in both the community and hospital settings with

>60% of community CSSI in the USA were caused by MRSA with higher rates in the south of the country [2].

It has been estimated that 570,000-600,000 patients were hospitalized in the USA with a principal diagnosis of CSSI, these infections generally lead to a hospital stay of 4.5 days. Approximately half of these infections are caused by *S aureus* thus approximately 150,000 patients are hospitalized with a MRSA CSSI as an initial diagnosis [3]. The overall costs of treating skin infections is driven by the need for admission which according to Labreche et al [4] using the HCUP database estimate hospital admission for CSSI to be \$17,591 assuming a 10 day stay. ER visit, incision and drainage and standard antibiotic therapy costs to hospital stay adds a further \$2,900 leading to a total of almost \$20,000 per hospitalized CSSI. Failure of initial therapy further compounds these sums. In Europe Eckman et al [5] studied the management of CSSI across 12 European countries and observed that early switch from IV to oral therapy, quicker discharge from hospital and awareness of local antibiotic susceptibility among usual CSSI pathogens all contribute to marked savings of €414 in Slovakia to €2,703 in France. Again highlighting the impact of hospital admission to overall costs of CSSI management. Finally from Greece Athanaskis et al [6] estimated the national inpatient costs of CSSI to be €29,196,218 in 2013.

These authors described a budget impact analysis which calculated the cost per day of hospitalization, drug costs in terms of base price and then frequency per day and then usual

duration of therapy. The price per day to treat a patient with CSSI was €189.20 (\$231.4). Thus avoidance or shortening of hospitalization is economically sound as long as efficacy was maintained and the cost of antibiotics played a small role in the overall costs of treating CSSI.

The treatment of skin and skin structure infections, including MRSA, was the subject of a recent guideline published by the Infectious Disease Society of America (IDSA) [7] which recommended mainly intravenous antibiotics with only linezolid being available as both IV or oral delivery.

However 2014 was a watershed year in the USA with 3 new parenteral, dalbavancin, oritavancin and ceftolazane/tazobactam and one IV/oral agent, tedizolid were approved by the FDA. The new cephalosporin was not approved for skin infections. These advances were based on exploitation of drug pharmacokinetics which achieved desirable clinical efficacy against the key pathogen MRSA [8]. These advances to the CSSI armamentarium are summarized in Table. Prior to antibiotics the management of skin infections such as furunculosis or carbuncles required careful washing, bed rest and a variety of chemical approaches some of which are now known to be toxic. Interestingly use of staphylococcal toxoid was associated with a clinical improvement. The early antibiotics needed to be given multiple times a day for long

periods, probably based on concerns about drug safety or resistance development or perhaps manufacturing issues rather than based on efficacy criteria. Today we often use parenteral antibiotics given 2-4 times a day for 10-14 days. However a decade ago linezolid (100% bioavailable drug) was approved for CSSI at a dose of 600mg bid for 7-10 days. In 2010 ceftaroline was approved as an IV bid drug for CSSI with a standard course regimen i.e. twice daily for 10-14 days.

But in the past year three drugs, tedizolid, dalbavancin and oritavancin have all been approved for CSSI/ABSSSI in the USA. Each brought novel attributes to the management of these infections. Table 2 highlights the key features of these agents but what is not presented is the fact that the two latter glycopeptides actually provide the opportunity to diagnose and treat the patient without having to admit them, thus creating a significant potential cost saving.

The management of less serious or uncomplicated skin infections in the community is at a tipping point where “old” agents (e.g. clindamycin, doxycycline and trimethoprim-sulphamethoxazole) are being revisited as anti-MRSA drugs. Perhaps with the approval of infrequent or especially single dose efficacious safe therapies for MRSA we may be at a similar “tipping point” for complicated skin infections?

Table:

Therapy	Year	Dose	Regimen	Comments
Pre antibiotics	1928	Incision & drainage plus 15% ethyl alcohol plus 1:500 mercury bichloride or 25% ichthyol dressings or 5-10% ammoniated mercury. (1)	NA	Lack of antimicrobials meant use of chemicals to treat all infections, many were highly toxic [8]. The reference tells a dramatic tale of how penicillin changed patient's lives so quickly.
Penicillin	1942	250-500mg	3 or 4 x day for 10d	The first antibiotic to be used in human skin infections, notably in Boston US [9].
Vancomycin	1960	15-20mg/kg/dose	3 or 4x/day 10-14d	Developed as an alternative to penicillins for <i>S aureus</i> infections. Initial issues with quality leading to major allergic reactions. Concern over renal toxicity still an issue [10].

Oxacillin	1988	500mg	4x/day – 7 day	B-lactam chemically modified to be active against methicillin resistant <i>Staphylococcus aureus</i> [11].
Linezolid	2003	600mg	2x/d 10-14d	A novel class with IV & PO options active vs MRSA but cannot use for >14 days as toxic to marrow [12].
Ceftaroline	2014	600mg	2x d 5-14d	Notable as first B lactam active vs MRSA but IV only [13].
Dalbavancin	2014	1000mg day1 500mg 2 nd dose	2 doses 7 days apart	Long half-life glycopeptide with safer profile than vancomycin, approved for 2 doses a week a part [14].
Oritavancin	2014	1200mg	Single dose	Even longer half-life so single IV dose is efficacious and as safe as, or better than other glycopeptides. May help avoid hospital admission thus avoiding possible hospital infections and lowering costs and maintaining efficacy [15].

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