



QUESTIONS AND ANSWERS FOR DIABETIC FOOT INFECTION PREVENTION PERSPECTIVES AND ITS COMPLICATION ASSOCIATED WITH DISEASES IN CLINICAL PRACTICE

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ABSTRACT

India has the largest number of persons suffering with diabetes all over the world. However, India leads the world with an estimated 41 million people with diabetes; this figure is predicted to increase up to 66million by 2025. Hence there is an urgency to develop the prevention of diabetic foot infection perspectives and its complication associated with diseases in clinical practice. For this purpose, we perform review of evidence. MEDLINE, PubMed, Cochrane Library, Dove Press and EMBASE were systematically searched for publications in English from 2005-2012. Reference lists and articles from the authors' libraries and older references generated from initial papers were also examined. Randomized clinical trials, longitudinal studies, case series and reports from regulatory agencies were considered if appropriate. The questions and answers were reported in text supporting level of evidence (ie) reference. Most frequently asked question discussed in this review, we have to perform SMART goal settings that are Specific, Measurable, Achievable, Relevant and Time-framed in diabetic patients. Meanwhile, educating about diabetic foot complication can save the limbs. Whereas, ongoing education for Health Care Professionals and the public statistical research can improve health care outcome.

Key words: Diabetes, Drugs, Infection, Education, Foot and Ulcer.

INTRODUCTION

Diabetes and its complications pose a major threat to future public health resources throughout the world [1]. Based on a compilation of studies from different parts of the world, the World Health Organization (WHO) has projected that the maximum increase in diabetes would occur in India [2]. It currently affects more than 194 million people worldwide and is expected to reach 333 million by 2025. India is considered as "Diabetic capital of the world", alone currently counts over 35 million people harbouring diabetes [3]. Foot disease is a common complication of type-1 and type-2 diabetes. Diabetic foot is a common cause for the hospital admissions of the diabetic patients in India. Diabetic foot as defined by the World Health Organization is, 'The foot of a diabetic patient that

has the potential risk of pathologic consequences, including infection, ulceration, and/or destruction of deep tissues associated with neurologic abnormalities, various degrees of peripheral vascular disease, and/or metabolic complications of diabetes in the lower limb'[2].

METHODS

The questions raised with the introduction of diabetic foot infection prevention perspectives and its complication associated with diseases in clinical practice. For this purpose, we perform review of evidence. MEDLINE, PubMed, Cochrane Library, Dove Press and EMBASE were systematically searched for publications in English from 2005-2012. Reference lists and articles from

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the authors' libraries and older references generated from initial papers were also examined. Randomized clinical trials, longitudinal studies, case series and reports from regulatory agencies were considered if appropriate. The questions and answers were reported in text supporting level of evidence (ie) reference.

Question 1: What are the prescribing indications for Tazira?

Piperacillin and Tazobactam (Tazira) for injection is indicated for the treatment of patients with moderate to severe infections caused by Piperacillin-resistant, Piperacillin/Tazobactam-susceptible, β -lactamase producing strains of the designated microorganisms in the specified conditions listed below:

- Appendicitis (complicated by rupture or abscess) and peritonitis are caused by piperacillin-resistant, β -lactamase producing strains of *Escherichia coli* or the following members of the *Bacteroides fragiles* group: *B. fragilis*, *B. ovatus*, *B. thetaiotaomicron*, or *B. vulgatus*.
- Uncomplicated and complicated skin and skin structure infections, including cellulitis, cutaneous abscesses and ischemic/diabetic foot infections are caused by piperacillin-resistant, β -lactamase producing strains of *Staphylococcus aureus*.
- Postpartum endometritis or pelvic inflammatory disease caused by piperacillin-resistant, β -lactamase producing strains of *Escherichia coli*.
- Community-acquired pneumonia (moderate severity only) caused by piperacillin-resistant, β -lactamase producing strains of *Haemophilus influenzae*.
- Nosocomial pneumonia (moderate to severe) caused by piperacillin-resistant, β -lactamase producing strains of *Staphylococcus aureus* and by piperacillin/tazobactam-susceptible *Acinetobacter baumannii*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Nosocomial pneumonia caused by *P. aeruginosa* should be treated in combination with an aminoglycoside). Piperacillin and tazobactam is indicated only for the specified conditions listed above. Infections caused by piperacillin-susceptible organisms, for which piperacillin has been shown to be effective, are also amenable to tazira treatment due to its piperacillin content. The tazobactam component of this combination product does not decrease the activity of the piperacillin component against piperacillin-susceptible organisms. Therefore, the treatment of mixed infections caused by piperacillin-susceptible organisms and piperacillin-resistant, β -lactamase producing organisms susceptible to tazira should not require the addition of another antibiotic.

It is useful as presumptive therapy in the indicated conditions prior to the identification of causative organisms because of its broad spectrum of bactericidal activity against gram-positive and gram-negative aerobic and anaerobic organisms. Appropriate cultures should usually be performed before initiating antimicrobial treatment in

order to isolate and identify the organisms causing infection and to determine their susceptibility to tazira. Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are known [4].

Question 2: What are the effective steps to be taken for dressing the wounds?

Wound dressings

Many dressings/applications are used in the management of diabetic foot ulceration. Dressing for the diabetic foot must include several of the following essential features:

1. Perform well in the enclosed environment of the shoe or boot and not take up too much space

Low/non-adherent dressings such as foams, alginates, tulle or Melolin would appear to fulfill these criteria, provided bulky secondary dressings are avoided. From a conformability point of view occlusive dressings/hydrocolloids are advantageous.

2. Be capable of absorbing large quantities of exudate and yet avoid plugging the wound and preventing drainage

Some non-adherent dressings are also relatively non-absorbent. Such is the case with Melolin for example, and its use should be avoided in sloughy/exudating wounds to prevent maceration. Packing should be avoided as it impairs drainage.

3. Not be associated with unwanted effects of dressing materials, do more harm than good if not used correctly

For example, inappropriate use of occlusive dressing, such as in the case of clinical infection with no systemic antibiotic therapy and/or inadequate wound assessment/surveillance.

4. Be comfortable and withstand the pressures and shear stresses of walking, without slipping, "bottoming out" or breaking

Lyfoam and Allevyn: 'sterile non-adherent dressings which stand up well to the pressures of walking'.

5. Not depend, for its optimal effect, on being left in place for longer than 24 hours

As diabetic foot lesions can deteriorate rapidly, it is essential for wounds to be/she checked every day or so and not left uninspected for long periods. This is particularly important for patients with neuropathy who have no protective pain sensation to warn them that a lesion is deteriorating.

6. Be capable of being easily and quickly lifted or removed for inspection; removable without causing damage to the wound

Traditional dry dressings have a tendency to adhere to the wound interface, causing trauma on removal. Minimum use of hypoallergenic tape and securing dressings, with a conforming bandage if skin is in poor condition, is important. Care not to apply bandages too tightly, or wrap

tape around toes, is also advised in order to minimize damage by constriction.

The information about wound dressings is summarized in the Table.1

Question 3: General procedure recommended before starting the treatment in diabetic foot infection patients?

Antibiotic selection

1. We recommend that clinically uninfected wounds should not be treated with antibiotic therapy (strong, low).
2. We recommend prescribing antibiotic therapy for all infected wounds, but caution that this is often insufficient unless combined with appropriate wound care (Strong, low).
3. We recommend that clinicians select an empiric antibiotic regimen on the basis of the severity of the infection and likely etiologic agent(s) (strong, low).
 - a. For mild to moderate infections in patients who have not recently received antibiotic treatment, we suggest that therapy just targeting aerobic GPC is sufficient (weak, low).
 - b. For most severe infections, we recommend starting broad-spectrum empiric antibiotic therapy, pending culture results and antibiotic susceptibility data (strong, low).
 - c. Empiric therapy directed at *Pseudomonas aeruginosa* is usually unnecessary except for patients with risk factors for true infection with this organism (Strong, low).
 - d. Consider providing empiric therapy directed against methicillin-resistant *Staphylococcus aureus* (MRSA) in a patient with a prior history of MRSA infection; when the local prevalence of MRSA colonization or infection is high; or if the infection is clinically severe (weak, low).
4. We recommend that definitive therapy be based on the results of an appropriately obtained culture and sensitivity testing of a wound specimen as well as the patient's clinical response to the empiric regimen (strong, low).
5. We suggest basing the route of therapy largely on infection severity. We prefer parenteral therapy for all severe, and some moderate, DFIs, at least initially (weak, low), with a switch to oral agents when the patient is systemically well and culture results are available. Clinicians can probably use highly bioavailable oral antibiotics alone in most mild, and in many moderate, infections and topical therapy for selected mild superficial infections (strong, moderate).
6. We suggest continuing antibiotic therapy until, but not beyond, resolution of findings of infection, but not through complete healing of the wound (weak, low). We suggest an initial antibiotic course for a soft tissue infection of about 1–2 weeks for mild infections and 2–3 weeks for moderate to severe infections (weak, low) [6].

Principles of Antibiotic Therapy for Diabetic Foot Infection

- Empiric antibiotic regimen should include an agent active against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* if necessary streptococci.
- Coverage for aerobic gram-negative pathogens is required for severe infection, chronic infection, or infection that fails to respond to recent antibiotic therapy.
- Necrotic, gangrenous, or foul-smelling wounds usually require anti-anaerobic therapy.
- Initial empiric antibiotic therapy should be modified on the basis of the clinical response and culture or susceptibility testing.
- Virulent organisms, such as *S. aureus* and streptococci, should always be covered in polymicrobial infection.
- Coverage for less virulent organisms, such as coagulase-negative staphylococci, may not be needed.
- Parenteral antibiotics are indicated for patients who are systemically ill, have severe infection, are unable to tolerate oral agents, or have infection caused by pathogens that are not susceptible to oral agents.
- Using oral antibiotics for mild to moderate infection and switching early from parenteral to oral antibiotics with appropriate spectrum coverage and good bioavailability and tolerability are strongly encouraged.
- Although topical antibiotics can be effective for the treatment of mildly infected ulcers, they should not be routinely used.
- Discontinuation of antibiotics should be considered when all signs and symptoms of infection have resolved, even if the wound has not completely healed.
- Cost should be considered when selecting antibiotic therapy.

Piperacillin-tazobactam is a b-lactam with a wide in vitro spectrum of activity, comparable to that of imipenem and greater than that of ceftazidime. Furthermore, it is stable in saline solution for 24 h at room temperature and for 7days when refrigerated at 5°C. Because of its antimicrobial spectrum, its use in monotherapy, and its stability, piperacillin-tazobactam is a good antibiotic for treating infections in which multiple organisms, anaerobic and/or aerobic, are suspected. Piperacillin-tazobactam 3.375 to 4.500 g IV every six to eight hours used to treat severe infections and in moderate infections when the probable pathogen is *Pseudomonas aeruginosa* [7].

Question 4: What is the role of microbiologist in treating diabetic foot infections?

As microbiologist has specialist knowledge necessary for infection control and antibiotic use he/she is an indispensable member of ICC/ICT and AC in hospitals. Other members of ICC and AC in hospital do not have the knowledge of microbiology. It is not surprising then, that in US almost half of the ICC chairs are laboratory personnel.

It is also important that the microbiologist is a medical doctor, because he/she will thus understand

pathogenesis of infection as well as pathogenesis of HAI, not only characteristics of an organism, will be able to understand pharmacokinetics and pharmacodynamics of antimicrobial agents - and will be able to communicate with clinical and nursing colleagues on the same level of understanding disease, therapy and epidemiology. Only exceptionally, if there is no medical doctor available, a properly educated scientist could be microbiologist too, but in that situation he/she has to be very closely connected with infectious disease specialist [8].

Role of nutrition in wound healing?

There is no specific recommendation for optimal blood glucose or hemoglobin A1c level to promote wound healing. According to the 2009 Standards of Medical Care in Diabetes, lowering HbA1c to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Without specific guidelines for blood glucose control to promote wound healing, it makes sense to set a goal for HbA1c below 7%.

Medical nutrition therapy (MNT) for wound healing in people with diabetes includes the following four areas:

1. Thirty to 35 kcal/kg body weight, adjusted based on changes in weight and wound healing:

According to Collins, calorie intake is the most important component of nutrition care for wound healing. Without optimum calorie intake, protein will not be available to promote wound healing, and vitamin and mineral intake will most likely be suboptimal. Collins explains that wound healing itself is an energy-intensive, anabolic process that demands optimal calorie intake.

2. 1.25 to 1.5 g protein/kg body weight to achieve a positive nitrogen balance:

Renal function should be regularly assessed to ensure appropriate protein intake.

3. Thirty ml fluid/kg body weight to prevent dehydration:

Increased amounts of fluids may be necessary with elevated temperature, vomiting, profuse sweating, diarrhea, or heavily draining wounds.

4. Encourage a balanced diet that meets the RDA for all vitamins and minerals:

Becky Dorner, RD, LD, president of Becky Dorner & Associates, Inc and Nutrition Consulting Services, Inc and a coauthor of the NPUAP white paper, notes that there is no research to support higher doses of vitamins or minerals. Collins agrees but notes that we may never have evidence-based guidelines giving specific micronutrient recommendations to promote wound healing because of the difficulty and expense of this type of research.

5. Supplemental Nutrition

Supplements may be required to meet calorie and protein needs in some people and can include homemade high-protein/high-calorie shakes or specialized commercial formulas such as Boost, or similar products.

Arginine is an amino acid normally produced in adequate amounts in the body. However, stress or illness may require increased amounts of arginine from the diet. Collins suggests a 30-day trial period of arginine to promote wound healing but warns that adequate calorie and protein intake must be the first priority. Patients with marginal nutrition status and intake will benefit from a multivitamin and possibly from an additional zinc and vitamin C. However, there are no established guidelines for micronutrient supplementation in diabetic wounds [9].

Question 5: What are the preventive steps to be taken to avoid recurrence?

The first step in the prevention of any neuropathic ulcer is restriction of weight bearing of the involved extremity.

- Patients with limb-threatening foot infections and noncompliant patients will require hospitalization and bed rest, followed by evaluation and management of arterial ischemia.
- Uncomplicated neuropathic ulcers will often heal with topical therapy and nonweight bearing, and a trial of outpatient care is warranted.
- Topical dressings should be aimed at maintaining a moist environment with saline impregnated gauze, topical antibiotic ointments, or other similar agents.
- The ulcer should be protected from excessive pressure by placing of an accommodative pad around the lesion to distribute pressure to surrounding tissues.
- Heavy callus around the edges of the lesion should be trimmed away to reduce peak plantar pressure, and shoes should be replaced with a stiff-soled “healing sandal.”
- Custom-molded orthotics and extra-depth shoes, running shoes, or custom-molded shoes in the case of severe foot deformity, are also prescribed to prevent future recurrence.
- Hyperbaric oxygen therapy has received much attention in recent years as an adjunct to facilitate wound healing for diabetic foot ulcers and thus lower amputation rates [10].

Question 6: What is recommended for the verifying adherence?

There are many methods of tracking adherence on a day – to- day basis. An increasing variety of pill containers, both for research purposes and popular consumer use, allow for the electronic recording of the opening of the container or the removal of the pill. Still, these devices do not prove ingestion. In most cases, such devices do not even confirm that there is actually medication in the container, whether or not these various devices significantly improve upon simple self-reporting methods is debatable.

For rare cases in which actual proof of pill ingestion is required, there is a number of competing startup companies with various versions of a “chip-on –a-

pill” technology, in which a signal is sent from the chip to a sensor once degraded within the stomach. This technology will likely be most relevant and feasible for use in rigorous clinical trails, where intentional or unintentional non adherence by a subject could critically impact trail results. This technology may also be a more cost effective alternative to having a nurse or other clinical trial professional observe daily ingestion, a method used in selected circumstances [11].

Question 7: Could you tell me any other wound therapy in salvaging the diabetic foot?

Negative pressure wound therapy was first investigated by Morykwas and Argenta et al in 1997. The technique of NPWT is very simple. Proprietary foam with an open cell structure is introduced into the wounds and the wound drain with lateral perforations is laid on top of it. The entire area is then covered with transparent adhesive membrane, which is firmly secured to the healthy skin around the wound margin. When the exposed end of the drain tube is connected to vacuum source, fluid is drawn from the wound through the foam and evacuated into a reservoir for subsequent disposal [12].

NPWT helps in wound healing by removing the interstitial fluid, increasing the blood flow and decreasing the tissue bacterial level. It has since been proposed that application of sub atmospheric pressure produces mechanical deformation or stress within the tissue, resulting in protein and matrix molecule synthesis and enhanced angiogenesis. From various studies, it has been shown that a negative pressure value of 125mmHg appears to be optimum when applied in a cyclical fashion. NPWT therapy has also been shown to be cost effective in use [13]. Numerous literature have described the use of NPWT in the treatment of a variety of wound types including extensive degloving injuries, infected sternotomy wounds and various soft tissue injuries prior to surgical closure, grafting or reconstructive surgery. Banwell et al have found that immediate application of NPWT following injury/debridement produced good results. [14]

Question8: What are the risk factors for peripheral arterial disease (PAD) ?

Diabetes mellitus is associated with a near 3-fold increased risk of accelerated atherosclerosis, which is diabetic population. This underlines the importance of identifying and aggressively managing associated vascular risk factors, such as obesity, cigarette smoking, dyslipidemia, hypertension, and sedentary behavior [15].

Question 9: How would evaluate cost-effectiveness of interventions in diabetic foot disease?

Most studies explore results from predictive models, with the most common being the Markov model. This can be useful mathematical tool for obtaining a projection of costs and effects of an intervention. This

method for modeling diseases, such as diabetic foot ulcers, is relevant because it can take into account the chronicity of the disease and the occurrence of the same events more than once. However, data from these studies are difficult to compare owing to differences in demographics and health care system [16].

Question 10: How do you measure direct costs in any disease condition?

Direct economic costs of disease are those generated by the resources used in treating or coping with a disease, including expenditures for medical care and the treatment of the illness (hospital care, physician services, nursing home care, drugs, , transportation costs, costs of care-giving by family members are also included [17].

Question 11: Mention the role of bee honey dressing in the treatment of diabetic foot ulcers?

Honey dressing was applied to wounds for 3 months till healing, grafting in developing countries. It is an environmentally based cost and clinically effective dressing. More importantly, it is very safe as it did not result in any complication (local or systemic) or emergence of resistant bacterial strains. Nevertheless, it is not effective in cases of severe vascular compromise, exposed bone (without periostium) or established osteomyelitis [18].

Question12: Common pathogens in diabetic foot infection?

Staphylococcus aureus and β -hemolytic streptococci are the first microorganisms to colonize and acutely infect breaks in the skin. Chronic wounds develop a more complex polymicrobial microbiology, including aerobic gram negative rods and anaerobes. Gram-negative bacilli mainly *Enterobacteriaceae*, are found in many patients with chronic or previously treated infections, and *Pseudomonas aeruginosa* is specifically associated with wounds treated with wet dressings [19]. Less virulent bacteria such as *Enterococcus* spp. Coagulase-negative *Staphylococcus* spp. or *Corynebacterium* spp. may also represent true pathogens. Anaerobes are rarely the sole pathogen, but they often participate in a mixed infection with aerobes, especially in cases of deep tissue infection , these mixed infections provide an optimal opportunity for microbial synergy, which increases the net pathogenic effect and hence the severity of infection [20].

Question 13: How do you evaluate wound in diabetic foot infection?

Wound evaluation (“extent/size” and “depth/tissue loss items” in the Perfusion, Extent/size, Depth/tissue loss, Infection and Sensation (PEDIS System)) includes the evaluation of the size and depth of the wound, both of which should be determined after debridement. The Size could be evaluated using a precise technique (planimetry or grid technique), however, this is not always possible in

clinical practice. Instead, wound size and depth can be estimated by multiplying the largest diameter by the perpendicular largest diameter [21]. Ulcer depth should be evaluated related to the structures involved. Ulcers are divided into lesions confined to the skin, those penetrating to the subcutaneous structures (fascia, muscle, or tendon) and those involving subsequent layers of the foot (bone and/or joint).

Question 14: How do you minimize the complication of diabetic foot ulcer?

Patients education and understanding of the nature of treatment of neuropathic complications on the part of physician can avert many of these complications. Implementation of novel therapeutic strategies, wider availability of multidisciplinary foot care teams, as well as improvement of scientific research are needed in order to minimize the foot complications [22].

Table 1.Types of dressing Uses

Non/Lowadherent dressings e.g.Melolin	Suitable for dry wounds and lightly exudating wounds
Semi-permeable films e.g.Tegaderm Bioclusive	Suitable for relatively shallow wounds.Also used as secondary dressings to retain another product in the wound, Excessive exudates may accumulate under the film
Paraffin tulle (non-medicated) e.g. jelonet (paraffin)	Suitable for clean, superficial wounds
Tulle (medicated) e.g.Bactigra-Chlorhexidine 0.5%	Infected superficial wounds
Inadine –Povidone- Iodine (1% available iodine)	Clinically infected wounds should be treated with an appropriate systemic antibiotic
Hydrogels	Suitable for desloughing and for light to medium exuding wounds Require a secondary dressing
Hydrocolloids Corn feel	Suitable for desloughing and for light to medium exuding wounds Waterproof- require no secondary dressings
Kaltostat (Calcium-Sodium alginate)	Suitable for exuding wounds, only sorbsan forms a soft flexible gel ,whilst kaltostat forms a firmer gel
Foams (e.g. Lyofoam)	Suitable for exuding wounds

CONCLUSION

Most frequently asked questions discussed in this review, we have to perform a SMART goal setting that is Specific, Measurable, Achievable, Relevant and Time-framed in diabetic foot infection patients. Meanwhile,

educating about diabetic foot complication can save the limbs. Whereas, on-going education for Health Care Professionals and the public statistical research can improve health care outcome.

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