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The Use of Antibiotics in Chronic Wounds

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Professor David Leaper in his paper Approach to chronic wound infection states

“Infection is the likeliest single cause of delayed healing in healing of chronic open wounds by secondary intention. If neglected it can progress from contamination to colonization and local infection through to systemic infection, sepsis and multiple organ dysfunction syndrome, and it can be life-threatening.

The continuing rise of antimicrobial resistance to antibiotics should lead us to reserve their use for these indications, as no new effective antibiotics are in the research pipeline”

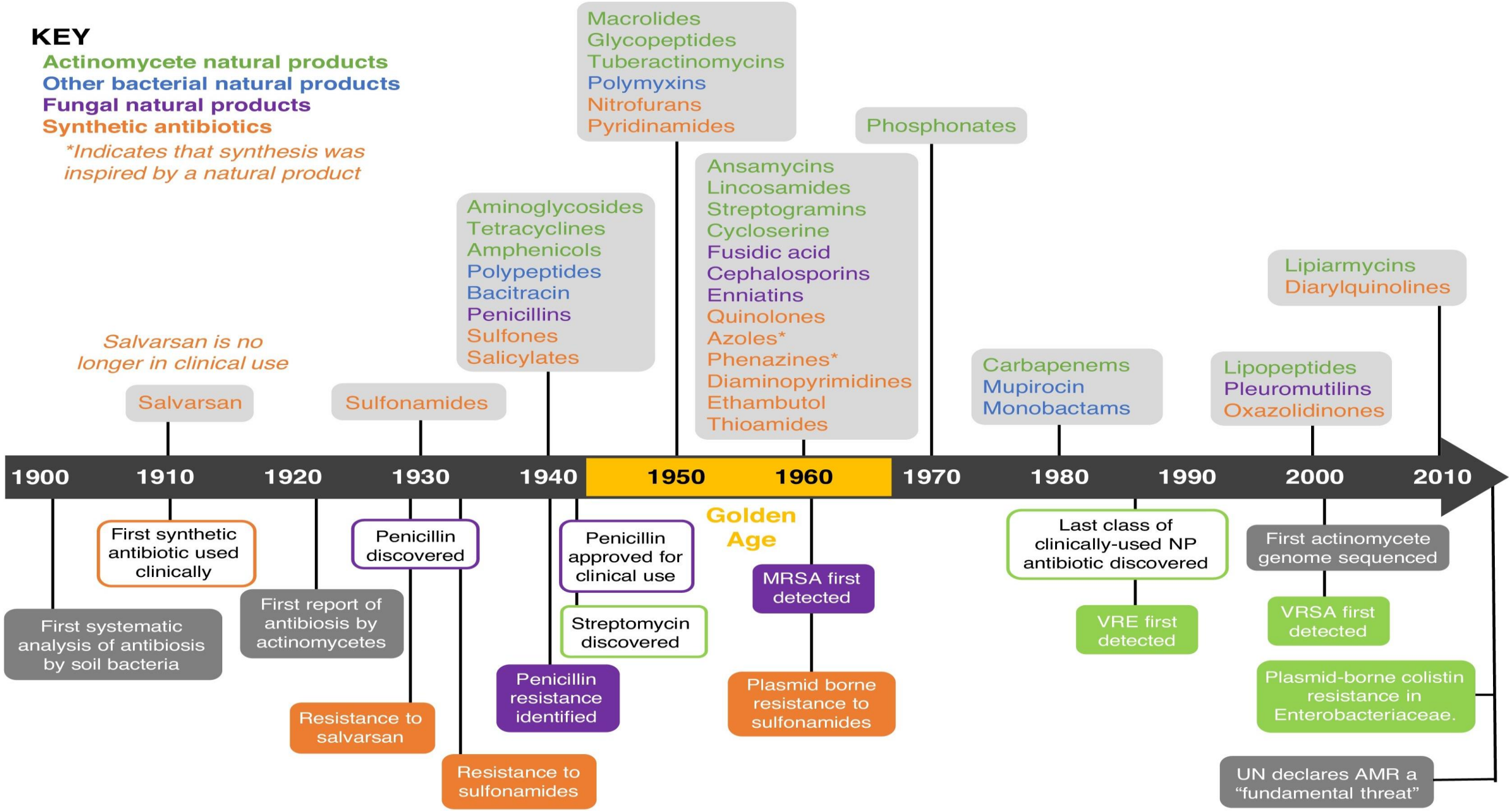
D. Leaper, O. Assadian and C.E. Edmiston Approach to chronic wound infections British Journal of Dermatology (2015) 173, pp351–358

What are Antibiotics

An antibiotic is an antimicrobial substance active against bacteria. It is the most important type of antibacterial agent for fighting bacterial infections. Antibiotic medications are widely used in the treatment and prevention of such infections. They may either kill (Bactericidal) or inhibit the growth of bacteria (Bacteriostatic).

Antibiotics (such as penicillin) are those produced naturally (by one microorganism fighting another), whereas nonantibiotic antibacterials (such as sulfonamides) are fully synthetic. Semi-synthetic drugs are neither completely natural nor completely synthetic. They are a hybrid. Semi-synthetic drugs are generally made by converting starting materials from natural sources into final products via chemical reactions.

However, the effectiveness and easy access to antibiotics have also led to their overuse and some bacteria have evolved resistance to them.


KEY
Actinomycete natural products
Other bacterial natural products
Fungal natural products
Synthetic antibiotics
*Indicates that synthesis was inspired by a natural product
Macrolides
Glycopeptides
Tuberactinomycins
Polymyxins
Nitrofurans
Pyridinamides
Phosphonates
Ansamycins
Lincosamides
Streptogramins
Cycloserine
Fusidic acid
Cephalosporins
Enniatins
Quinolones
Azoles*
Phenazines*
Diaminopyrimidines
Ethambutol
Thioamides
Aminoglycosides
Tetracyclines
Amphenicols
Polypeptides
Bacitracin
Penicillins
Sulfones
Salicylates
Lipiarmycins
Diarylquinolines
Salvarsan is no longer in clinical use
Salvarsan
Sulfonamides
Carbapenems
Mupirocin
Monobactams
Lipopeptides
Pleuromutilins
Oxazolidinones
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
2010
Golden Age
First systematic analysis of antibiosis by soil bacteria
First synthetic antibiotic used clinically
First report of antibiosis by actinomycetes
Penicillin discovered
Resistance to salvarsan
Resistance to sulfonamides
Penicillin resistance identified
Penicillin approved for clinical use
Streptomycin discovered
MRSA first detected
Plasmid borne resistance to sulfonamides
Last class of clinically-used NP antibiotic discovered
VRE first detected
First actinomycete genome sequenced
VRSA first detected
Plasmid-borne colistin resistance in Enterobacteriaceae.
UN declares AMR a "fundamental threat"
Current Opinion in Microbiology

Narrow-spectrum and broad-spectrum antibiotics

A broad- spectrum antibiotic is one that acts on the two major bacterial groups, Gram Positive and Gram Negative or any antibiotic that acts against a wide range of disease-causing bacteria These medications are used when a bacterial infection is suspected but the group of bacteria is unknown (called empiric therapy) or when infection with multiple groups of bacteria is suspected. This is in contrast to a narrow spectrum antibiotic, which is effective against only a specific group
of bacteria Although powerful, broad-spectrum antibiotics pose specific risks, particularly the disruption of native, normal bacteria and the development of antimicrobial resistance.

Broad Spectrum

- Doxycycline.
- Minocycline.
- Aminoglycosides (except for streptomycin)
- Ampicillin.
- Amoxicillin/clavulanic acid (Augmentin)
- Carbapenems (e.g. imipenem)
- Piperacillin/tazobactam.

Narrow Spectrum

- Azithromycin.
- Clarithromycin.
- Erythromycin.
- Clindamycin.
- Older penicillins (penG)
- Macrolides
- Vancomycin

ANTIBIOTICS: MODES OF ACTIONS

1. **Inhibition of cell wall synthesis** eg, penicillins, cephalosporins, vancomycin, bacitracin, novobiocin

2. **Inhibition of cell membrane function** eg, polypeptides (polymyxin, colistin), tyrothricin, polyenes (amphotericin, nystatin), itra-, keto-, fluconazole, terbinafine, amorolfine

3. **Inhibition of nucleic acid synthesis** eg, actinomycin, mitomycin, colicin, quinolones, griseofulvin, ethambutol, rifamides, isoniazid.

4. **Inhibition by competitive inhibition** eg, sulfonamides, para-aminosalicylate, dapsone, 5-flucytosine, nitrofurantoin

5. **Inhibition of protein synthesis** eg , chloramphenicol, tetracyclines, macrolides, lincosamides, aminoglycosides, linizolid.

Hazards of antimicrobial therapy

1. Allergic reactions (type I), eg, penicillins, sulfonamides, many others
2. Superimposed infections with broad- spectrum antibacterials
3. Moniliasis with broad-spectrum antibacterials
4. Gastrointestinal tract upset including mild diarrhoea (very common)
5. Blood dyscrasias, eg, chloramphenicol, sulfonamides, etc
6. Neurotoxic effects, eg, aminoglycosides, fluoroquinolones

Hazards of antimicrobial therapy

7. Nephrotoxic allergic reactions, eg, aminoglycosides, cephalosporins, bacitracin

8. Pseudomembranous colitis, more common with lincosamides and cephalosporins

9. Interactions with other drugs eg, flouroquinolones, macrolidess, tetracyclines, itra-, keto- and fluconazole, rifampicin, rifabutin

10. Contraindicated in pregnancy (Categories, C, D, X)

Combined antibiotic therapy: Indications

1. To achieve broad spectrum cover pending culture results
2. In mixed infections due to organisms of mixed susceptibilities
3. Enhanced inhibition or killing power: eg, inactivation of drug-destroying enzymes
4. To prevent or delay emergence of resistant organisms
5. To allow a lower dose of shorter course or a toxic drug.

Contraindications

Combining bactericidal and bacteriostatic antibiotics is not advisable
if bactericidal drugs are most potent with actively dividing cells, then the inhibition of growth induced by a bacteriostatic drug should result in an overall reduction of efficacy when the drug is used in combination with a bactericidal drug.

Critical Issues in the Selection of Antibiotics for Treating Wound Infections

Site/type of infection
Drug characteristics
Penetration
Dose
Duration
Route
Combination
Pharmacokinetics/Pharmacodynamics
Toxicity

The success of an antibiotic will depend on not only the susceptibility of the organisms to a drug but also to the ability of the drugs to penetrate the site of the infection.
Drug concentration will vary with the site of the infection bone in particular does not achieve good Drug levels compared with more vascular tissue.

The level of protein binding of the drug will also impact on the concentration of drug at the site of the infection it is important to note that a bound drug is inactive

Selection of therapy

Empiric→ Directed/Guided

- Based on preliminary culture details
  - Gram (+) cocci, coagulase (+) in a surgical wound in a hospital may be MRSA, likely sensitive only to vancomycin

Directed/Guided Therapy

- Based on culture and sensitivity results
  - Enterococcus faecium, sensitive to ampicillin, piperacillin and vancomycin, HLS with gentamicin

Antibiotics are an essential treatment modality for a range of infections and their use has resulted in life saving outcomes. However their administration in the 20th/21st century has resulted in a significant overprescribing there are many reasons including patient pressure, non adherence to Antibiotic use guidelines or a lack of understanding of infection.

There are many published studies which examined this issue and report on the misuse and or overprescribing of Antibiotics.

What is the greatest risk to the world today Climate Change ?

What is the greatest risk to the world today

No

it is Antibiotic Resistance

What is antimicrobial resistance?

- Antimicrobial resistance (AMR) is the ability of a microorganism (like bacteria, viruses and parasites) to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it. As a result, standard medical treatments become ineffective and infections persist and may spread to others. Health care professionals are left with limited or in some instances, no available treatment options.

Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum

Antimicrobial resistance is now a global threat. Its emergence rests on antimicrobial overuse in humans and food-producing animals; globalization and suboptimal infection control facilitate its spread. While aggressive measures in some countries have led to the containment of some resistant gram-positive organisms, extensively resistant gram-negative organisms such as carbapenem-resistant entero bacteriaceae and pan-resistant Acinetobacter spp. continue their rapid spread.

Huttner et al. Antimicrobial Resistance and Infection Control 2013, 2:31

Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated Infections Forum

Antimicrobial conservation/stewardship programs have seen some measure of success in reducing antimicrobial overuse in humans, but their reach is limited to acute-care settings in high-income countries. There is scant or no oversight of antimicrobial administration to food-producing animals, while evidence mounts that this administration leads directly to resistant human infections.

Huttner et al. Antimicrobial Resistance and Infection Control 2013, 2:31

Because of increasing antimicrobial resistance and the shortage of new antibiotics, there is a growing need to optimize the use of old and new antibiotics. Modelling of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of antibiotics can support the optimization of dosing regimens. Antimicrobial efficacy is determined by susceptibility of the drug to the microorganism and exposure to the drug, which relies on the PK and the dose.

Antimicrobial resistance kills

Infections caused by resistant microorganisms often fail to respond to the standard treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk of death.

As an example, the death rate for patients with serious infections caused by common bacteria treated in hospitals can be about twice that of patients with infections caused by the same non-resistant bacteria. MRSA (methicillin-resistant *Staphylococcus aureus*, in the community and in hospitals) are estimated to be 64% more likely to die than people with a non-resistant form of the infection.

Present situation Resistance in bacteria

WHO’s 2014 report on global surveillance of antimicrobial resistance reveals that antibiotic resistance is no longer a prediction for the future; it is happening right now, across the world, and is putting at risk the ability to treat common infections in the community and hospitals. Without urgent, coordinated action, the world is heading towards a post-antibiotic era, in which common infections and minor injuries, which have been treatable for decades, can once again kill.

Traditional antibiotic therapy, which has been administered predominantly intravenously and frequently for several months, this can often be replaced by appropriately selected oral antibiotic regimens following only a brief (or even no) parenteral therapy, and given for no more than 6 weeks.

New ways to use old antibiotics, as well as new antimicrobial agents and approaches make us optimistic about achieving even better outcomes in the next few years.

Lipsky, B.A.; Uçkay, ˙I. Treating Diabetic Foot Osteomyelitis: A Practical State-of-the-Art UpdateMedicina 2021, 57, 339

Antibiotic Stewardship

- The CDC estimates that half of antibiotic use is unnecessary. Stewardship programs should be developed and used to optimize the use of antibiotics. Although this is currently happening, the CDC calls for acceleration in the implementation of these efforts.
- Until recently, there has been a steady pipeline of antibiotics entering the marketplace. Unfortunately, at this point, new drugs may be a decade away.
- The report includes descriptions of bacteria that cause human infections, as well as the antibiotics that are used to treat the infections. It does not include viral infections such as HIV and influenza or parasitic infections such as malaria.

Antibiotic Resistance Threats in the United States, 2013. CDC. Published online September 16, 2013.

Ten top tips to reduce Antibiotic Resistance

1. Develop new treatments almost 20 years, no new classes of antibiotics have been discovered
2. Provide education to prescribers and **consumers** on the benefits of judicious use of antimicrobial agents in wound care
3. Develop faster methods of identifying wound infection New and rapid methods are required to accurately identify infection
4. Use conservation programmes to address inappropriate use of antimicrobials
5. Develop and follow policy Controlling antibiotic resistance requires a multi-pronged approach

Sussman G Ten top tips: reducing antibiotic resistance Wounds International 2014 | Vol 5 Issue 4 |4-8

Ten top tips to reduce Antibiotic Resistance

6. Ensure facility cleaning and waste storage recommendations regarding cleaning of facilities where patient care is provided
7. Adopt management strategies for infected wounds All wound care must be performed using a high standard of infection control and prevention principles
8. Use risk assessment and management Managing risk must be a global response to the issue of antibiotic resistance
9. Employ wound cleansing
10. Improve population health and healthcare systems One of the most important methods of reducing antibiotic use and thereby resistance is by improving the general health of the population to reduce their need for hospitalisation

Sussman G Ten top tips: reducing antibiotic resistance Wounds International 2014 | Vol 5 Issue 4 |4-8

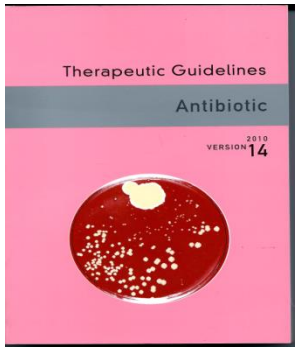
Use Therapeutic Guidelines: Antibiotic when prescribing antimicrobials

- Local guidelines should take into account recommendations in Therapeutic Guidelines: Antibiotic and also reflect local antimicrobial susceptibilities

- Consult the best available evidence and specialist clinicians for guidance on the management of infections not covered by guidelines

- Ensure guidelines are readily accessible wherever antimicrobials are prescribed

AUSTRALIAN COMMISSION ON SAFETY AND QUALITY IN HEALTH CARE



Prudent Use to ↓ Resistance

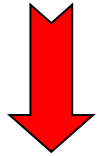
- Use antibiotics only when necessary
- Select agent with narrow spectrum
- Reserve broad spectrum agents for more resistant bacteria
- Continue for an “appropriate” duration
- Avoid chronic prophylaxis if possible
- Policy (guidelines, formulary, restrictions)
- Monitor trends in microbial sensitivity
- Pharmacokinetic/Pharmacodynamic Optimisation
- Cycling of antibiotics

Systematic Approach for Use of Antimicrobials

Confirm the presence of infection

Identification of the pathogen

Selection of therapy



Monitor therapeutic response

THE ANTIBIOTIC CREED

(*Antibiotic Guidelines* 16th edition 2019)

M I N D M E

M microbiology guides therapy whenever possible

I indications should be evidence-based

N narrowest spectrum required

D dosage appropriate to site & type of infection

M minimise duration of therapy

E ensure monotherapy in most situations

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Conclusion

The Antibiotic management of wound Infection should be systematic from the diagnosis of an infection, surgical intervention, if necessary, and choice of agent based on Micro identification of the organisms and their sensitivity.

Care must also be taken to ensure that the chosen agent reaches the site of infection in particular bone and consideration be given to patient factors such as renal function as this effects the excretion of the antibiotic.

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Thank You