

ANTIBIOTICS IN CRITICAL CARE: AN INTRODUCTION

ANAESTHESIA TUTORIAL OF THE WEEK 168

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QUESTIONS

- 1) Concerning cephalosporins, which of the following is correct?
 - a. Third generation have better activity against gram-positive organisms than first generation
 - b. Cefuroxime has robust activity against MRSA
 - c. Ceftazidime can be used for atypical pneumonias
 - d. They exhibit good CSF penetration
 - e. All work on an efflux protein in bacterial cell walls

- 2) Carbapenems:
 - a. Are beta-lactam antibiotics
 - b. Are useful in enterococcal infections
 - c. Are often paired with quinolones in cases of bowel perforation
 - d. Should be used first line in cases of coliform urosepsis
 - e. Are useful in pneumococcal infections

- 3) Pseudomonas Aeruginosa can be successfully treated with the following antibiotics:
 - a. Colistin
 - b. Cefuroxime
 - c. Ceftazidime
 - d. Gentamcin
 - e. Linezolid

- 4) Linezolid:
 - a. Has high bioavailability
 - b. Can cause bone marrow suppression
 - c. Is effective against vancomycin-resistant enterococcus (VRE)
 - d. Has activity confined to gram-positive organisms
 - e. Acts on a cell wall protein

- 5) Vancomycin
 - a. Is rapidly bactericidal
 - b. Is a first-line agent for methicillin-sensitive staph Aureus (MSSA)
 - c. Is effective against enterococcus
 - d. Is effective against coagulase-negative staphylococcus
 - e. Causes hypertension if rapidly infused

INTRODUCTION

This tutorial is intended as a basic overview of antibiotics with particular reference to critical care practice. It is not intended to be exhaustive but to serve as a “meet the drugs” introduction to 16 common drugs or drug classes. It is the first of three tutorials on the topic of intensive care microbiology; the second focuses on the detailed use, indications and side-effects of these drugs and the third looks at common ICU infections and their treatment- “meet the bugs”.

ANTIBIOTIC CLASSIFICATION AND MECHANISM OF ACTION

1. β -lactam antibiotics

This group has as its core the beta-lactam ring and includes the families of penicillins, cephalosporins, carbapenems and monobactams. Their antibacterial action depends on inhibition of the formation of peptidoglycan cross links in bacterial cell walls via the initial step of binding to a “penicillin binding protein”. They are therefore susceptible to B-lactamases produced by bacteria.

a. Penicillins

Bactericidal antibiotics, originally isolated from the mould *Penicillium notatum* by Fleming in 1929. Semisynthetic variants quickly followed, each with their own advantages, as detailed below.

Naturally –occurring: Penicillin V (Phenoxymethylpenicillin) and G (Benzyl Penicillin).

Penicillinase-resistant: Flucloxacillin.

Broader-spectrum penicillins: Amoxicillin, Ampicillin.

Penicillins combined with beta-lactamase inhibitors: Augmentin (amoxicillin/ clavulanate), Tazocin (piperacillin/ tazobactam), Timentin (ticarcillin/clavulanate)

Anti-pseudomonal penicillins: Piperacillin

Penicillins’ use in intensive care is generally for streptococcal, including enterococcal, or sensitive staphylococcal infections (MSSA) (flucloxacillin), initial treatment of e.g. community-acquired pneumonia (augmentin, currently) and first line for ventilator-associated pneumonia (tazocin) or neutropaenic sepsis (usually combined with an aminoglycoside for this indication).

b. Cephalosporins

Are originally derived from fungi of the species *Cephalosporium*.

They have innate beta-lactamase resistance and are bactericidal. They are conventionally divided into generations, as detailed below.

Successive generations manifest increasing activity against gram-negative organisms and, generally, less gram-positive activity.

First generation: cephalexin, cephadrine

Second generation: cefuroxime

Third generation: ceftriaxone, cefotaxime (poor activity against pseudomonas)

Third generation: ceftazidime (good anti-pseudomonal activity)

Fourth generation: cefpirome, cefipime

Fifth generation (emerging): ceftobiprole

The second and third generation cephalosporins’ status as workhorse hospital antibiotics is under threat in adults, particularly the elderly, due to the high rate of *C. Difficile* colitis and selection for MRSA. They are not generally used as single agents in the elderly for this reason. The fifth generation drug ceftobiprole, however, has good activity against MRSA as well as gram-negatives but is not in widespread use as yet.

c. Carbapenems

Imipenem, Meropenem, Ertapenem, Doripenem. These drugs are derived from species of *Streptomyces*. They are bactericidal and possess a very broad spectrum of activity, with good gram-positive, gram-negative and anaerobic cover. They are not active against MRSA and some enterococcal species, *Stenotrophomonas Maltophilia* or atypicals. They are beta-lactamase resistant, and currently one of the few options for treating extended-spectrum beta lactamase (ESBL) or AMP-C beta-lactamase producing Enterobacteriaceae. Imipenem is more renally-toxic than its congeners. Doripenem is a recent addition to the class which has better antipseudomonal activity and induces less resistance than its predecessors.

d. Monobactams

Aztreonam is currently the only commonly-used antibiotic in this class, which is based on a monocyclic beta-lactam ring derived from *Chromobacterium violaceum*. It acts on bacterial cell walls, in common with other beta-lactams, and is bactericidal. It is active against gram-negative bacteria only and is often used in place of broad-spectrum penicillins or cephalosporins because of allergy to these agents, since it exhibits low rates of cross-reactivity with them.

2. Macrolides

Erythromycin, Clarithromycin, Azithromycin. These drugs, originally derived from *Streptomyces erythreus*, consist of a macrolide ring with attached sugars.

They reversibly bind the bacterial 50s ribosomal subunit and inhibit bacterial protein synthesis. They are active against atypical bacteria such as mycoplasma, which lack a cell wall; and chlamydia, which is an intracellular organism. They also cover methicillin-sensitive staph. aureus (MSSA) and streptococci. They are bacteriostatic. As such their main use on ICU is in initial treatment of community-acquired pneumonia (CAP). They prolong the QT interval, similar to fluoroquinolones and care is needed when co-prescribed with other drugs which have similar effects.

3. Tetracyclines

Tetracycline, oxytetracycline, minocycline. These derivatives of naturally-occurring products of *Streptomyces* spp. are bacteriostatic and inhibit bacterial protein synthesis by binding to the 30S ribosomal subunit. They are effective against many gram-positive and gram-negative bacteria as well as Rickettsiae, atypical bacteria and some protozoa. Their use is uncommon in ICU practice, with the exception of their derivative tigecycline (see below).

4. Nitroimidazoles

Metronidazole affects DNA synthesis of bacteria and is bactericidal. It is used in anaerobic and protozoal infections, as well as orally or nasogastrically for the treatment of *Clostridium difficile*-associated diarrhoea. Resistance rates to metronidazole have remained consistently low in the UK and elsewhere.

5. Lincosamides

Clindamycin, Lincomycin. These antibiotics are derived from *Streptomyces Lincolnensis*. They act on the same receptor as the macrolides and may compete with them, but are not chemically similar. They are bacteriostatic and are useful in necrotizing soft tissue infections, mixed and anaerobic infections resistant to penicillins. They have a putative anti-exotoxin effect which renders them suitable for treatment of necrotising fasciitis caused by Group A streptococcus. *Clostridium difficile* diarrhoea was originally described in association with clindamycin usage and this remains a major source of concern.

6. Rifampicin

Rifampicin belongs to the rifamycin class of antibiotics. It works by inhibiting DNA-dependent RNA polymerase. It penetrates cells easily and its main use is as a component of therapy of tuberculosis. It is also used as therapy against gram-positive organisms such as streptococcus and staphylococcus, including MRSA; and as prophylaxis for contacts of patients with *Neisseria meningitidis* and *Haemophilus influenzae meningitis*.

7. Fusidic acid

This bacteriostatic agent inhibits bacterial replication by blocking RNA-transferase. It is mainly used as an adjunct in invasive staphylococcal infections, particularly in joints and bone. It is synergistic with rifampicin, but can counteract the effect of the quinolones.

8. Chloramphenicol

Is the only drug in its class and was synthesised originally from *Streptomyces venezuelae*. It is bacteriostatic and exerts effect by binding to the 50S ribosomal subunit of bacteria. It is useful in Salmonella infection, including typhoid, meningitis caused by haemophilus or meningococcus and cerebral abscesses (because of its excellent CSF penetration), and rickettsial infections. Its side-effects, notably aplastic anaemia, mean it is only rarely used in current ICU practice, but it remains a very valuable antibiotic in the developing world.

9. Aminoglycosides

Gentamicin, tobramycin and amikacin are aminoglycosides, derived from bacteria of the *Micromonospora* genus, which work via several different mechanisms:

Inhibition of bacterial protein synthesis, inhibition bacterial ribosomal translocation and disruption of the integrity of bacterial cell membrane. They have a spectrum of activity against gram-negative bacilli but also enterococcus and staphylococcus, including MRSA. They are usually administered in combination with a beta-lactam agent, especially where chest penetration is needed. They are extremely effective bactericidal antibiotics, but their nephro- and oto-toxicity are always grounds for concern in the ICU population. Peak levels correlate with efficacy; trough with toxicity. Inhaled tobramycin is used as an adjunct to systemic antibiotics for resistant gram-negative pneumonias in an effort to limit systemic toxicity while maintaining local delivery.

9. Fluoroquinolones

Ciprofloxacin, ofloxacin, moxifloxacin. These are synthetic antibiotics, derived from nalidixic acid, which is a urinary antiseptic referred to as a first-generation quinolone. Ciprofloxacin is a bactericidal antibiotic which exerts its effect by inhibiting bacterial DNA gyrase and topoisomerase 4, thus preventing replication. The quinolones are active against gram-negative bacteria, atypicals and some streptococci. They are less popular in UK ICU practice due to their propensity to select for MRSA and *Clostridium difficile*, and are generally used only in combination for this reason. Moxifloxacin's side-effect profile, particularly tendon rupture and QT prolongation, has resulted in more guarded second line use generally.

10. Polymyxin E

Colomycin or colistin is an antibiotic produced from the bacterium *Bacillus Polymyxa*. It binds to lipopolysaccharide in the bacterial cell wall and acts as a detergent, hydrolysing the cell membrane. It is active against gram-negative bacteria, including those resistant to other agents, such as pseudomonas and acinetobacter. Due to nephro- and oto-toxicity, attention has recently focused on inhaled colomycin as an adjunct to systemic antibiotics in the ICU setting, as well as in chronic medical conditions e.g. cystic fibrosis.

11. Trimethoprim- sulphamethoxazole (Septrin)

This combination drug consists of two agents which inhibit bacterial folate synthesis. It is used in the ICU context for three main indications; treatment of *Stenotrophomonas maltophilia* and *Burkholderia cephalica* infections and treatment and prophylaxis of *Pneumocystis Jiroveci* (PCP) pneumonia in the immunocompromised. It is toxic and can cause epidermal necrolysis as well as severe neutropaenia, particularly if the patient has been receiving immunosuppressants such as methotrexate which also have antifolate actions.

12. Glycopeptides

Teicoplanin and vancomycin inhibit bacterial cell wall synthesis. They are bactericidal but exhibit slow, time-dependent killing and have significant renal toxicity. Monitoring of levels is desirable with vancomycin. Infused too quickly, vancomycin can cause hypotension and "red man syndrome" due to histamine release. Their main use is in invasive staphylococcal infections, caused by *Staph Aureus*, *Staph epidermidis* and MRSA. Staphylococcal and enterococcal resistance to glycopeptides is growing and vancomycin-resistant and intermediate-staph aureus (VRSA and VISA) and vancomycin-resistant enterococcus (VRE) are emerging concerns in intensive care units. Newer agents in this category

include dalvabancin and telavancin.

13. Oxazolidinones

Linezolid inhibits bacterial protein synthesis at the 50s ribosome. It is active against gram-positive bacteria, including MRSA and VRE. It has high oral bioavailability, but potentially significant toxic effects. These include myelosuppression and thrombocytopenia (linezolid has some structural similarity to chloramphenicol), peripheral and optic neuropathy, lactic acidosis and monoamine oxidase inhibitor (MAOI)-like effects.

14. Lipopeptides

Daptomycin is a new agent isolated from the spores of *Streptomyces roseosporus*. It causes depolarisation of bacterial cell membranes and is rapidly bactericidal to gram positive organisms including MRSA and VRE. Peripheral neuropathy and myopathy are the major side-effects. It is not expected to be useful in pneumonia treatment due to poor lung penetration.

15. Streptogramins

Quinopristin-dalfopristin is a combination of two antibiotics of the streptogramin class. They are individually bacteriostatic but bactericidal when co-administered and act on the bacterial 50S ribosomal unit to prevent replication.

16. Tigecycline

This is an agent related to the tetracycline class, which is bactericidal. It has a wide spectrum of action on gram-positive and gram-negative bacteria with lack of cover for pseudomonas only. No dose adjustment is required in renal failure, making it an attractive choice in some ICU patients.

ANSWERS TO MULTIPLE CHOICE QUESTIONS

1. Cephalosporins
 - a. False
 - b. False. It can select for MRSA.
 - c. False
 - d. True
 - e. False. They act on cell wall proteins.

2. Carbapenems
 - a. True
 - b. False. This is a significant gap in their coverage.
 - c. False. A glycopeptide would be the logical combination to cover enterococcus species.
 - d. False. They are best kept in reserve in case of ESBL production by coliforms.
 - e. True. But first-line should be a narrower spectrum penicillin.

3. Pseudomonas Aeruginosa
 - a. True. Especially inhaled as an adjunct
 - b. False
 - c. True. This is antipseudomonal- but combination therapy is most frequently used.
 - d. True, but best combined.
 - e. False

4. Linezolid
 - a. True
 - b. True
 - c. True
 - d. True
 - e. False

5. Vancomycin
 - a. False. It is a slow killer, hence sometimes used in infusions.
 - b. False- flucloxacillin is better used first-line
 - c. True- but resistance is in the increase.
 - d. True
 - e. False- hypotension.

FURTHER READING

- Basic and Clinical Pharmacology. B.G. Katzung, ed. 11th edition. Lange 2007.
- Manual of Intensive Care Medicine. Irwin, R.S. and Rippe, J.M. ed. 4th edition. Lippincott Williams Wilkins 2006
- The Washington Manual of Critical Care. Kollef, M.H., Bedient, T.J., Isakow, W., Witt, C. ed. Lippincott Williams Wilkins 2008