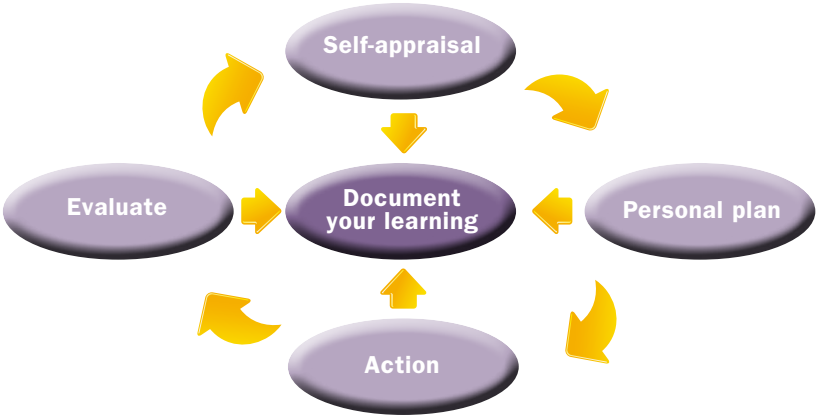


Antimicrobial Stewardship in Primary Care:

An Introduction to Antimicrobial Stewardship for Community Pharmacists

Welcome to the first in a three-part series of CPD articles on antimicrobial stewardship in primary care. This first article will focus on the following topics: the phenomenon of antimicrobial resistance, the principles of antimicrobial stewardship and the role of the community pharmacist in antimicrobial stewardship in primary care. Future articles will focus on an update on urinary tract infection management for community pharmacists and special populations in the context of antimicrobial stewardship.

Introduction

The gold standard and most widely used method for assessing bone mineral density (BMD) is the Dual Energy X-ray Absorptiometry (DEXA) scan. In general, the spine is the first region to lose a significant amount of bone mineral density. However, in some women, the first significant loss is in the hip region, and it is important that both hips are scanned in these circumstances as fractures of the hip have the highest morbidity and mortality rates. Osteoporosis is defined by a T-score value of the hips and lumbar spine from DEXA scanning *(Table 2)*.

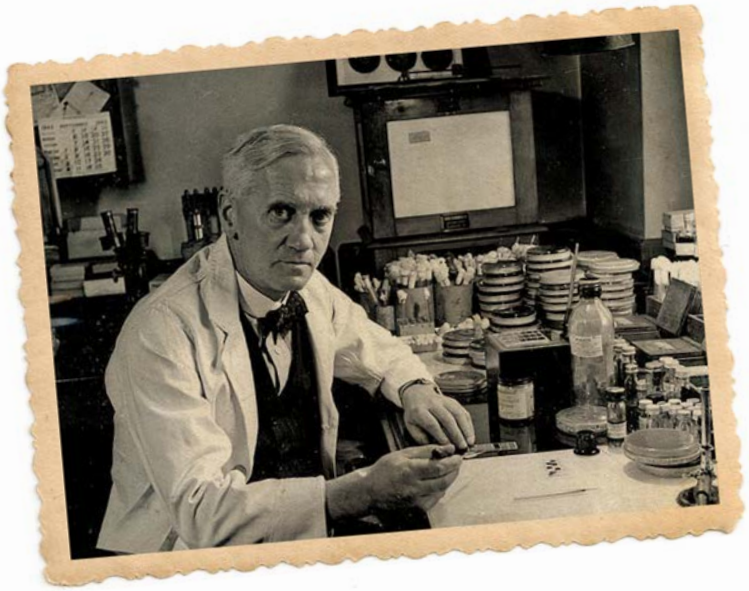
Antibiotics vs Antimicrobials

'Antimicrobials' is an umbrella term for antibiotics, antibacterials, antivirals, antiparasitic agents and antifungals. For the purpose of this article, the terms antibiotics and antimicrobials are used interchangeably.

It is important to note that the presence of a low trauma fracture constitutes a clinical diagnosis of osteoporosis regardless of a patient's T-score.

The introduction of penicillin to clinical practice in the 1940s is heralded as the dawn of the antibiotic era. This development is widely recognised as one of the greatest advances in modern medicine. Before its introduction, patients died from blood poisoning contracted from minor wounds, pneumonia, gonorrhoea and rheumatic fever in alarming numbers as there was no effective treatment for such infectious diseases. Today, we rely on antimicrobials to not only treat serious infections, but also to prevent infection in surgical patients, protecting immunocompromised patients and treating and preventing infection in animals, including livestock for human consumption.

Figure 1: **Alexander Fleming who, in 1928, discovered penicillin which was first used clinically in 1941**



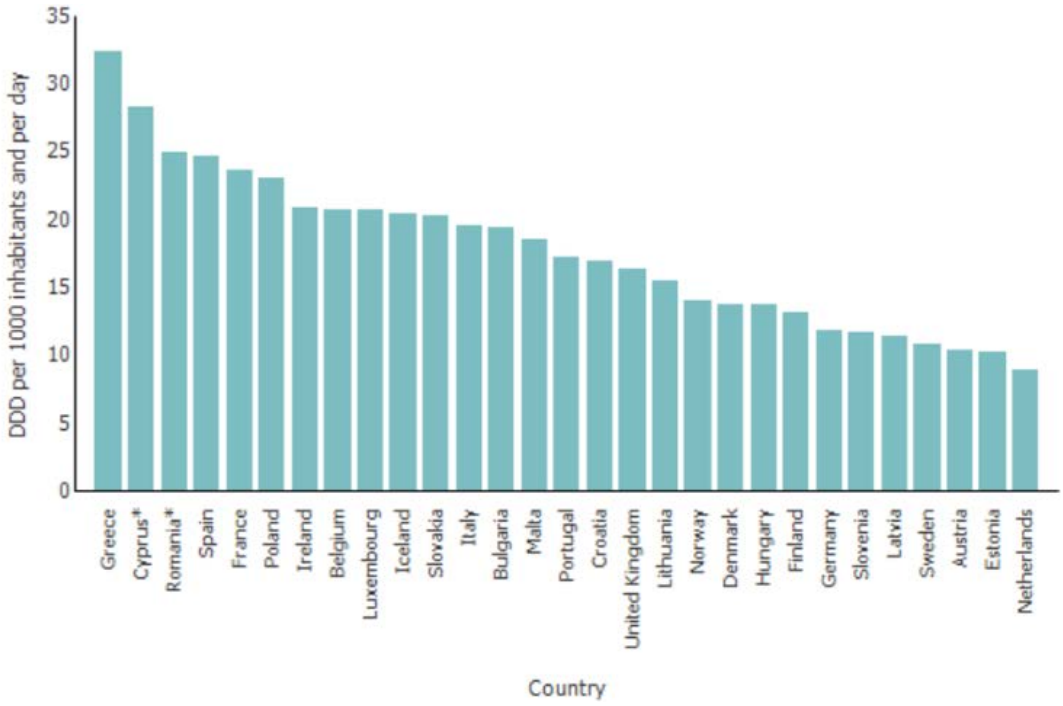
But with great power comes great responsibility! Alexander Fleming in 1945 warned of the need for appropriate use of penicillin in order to reduce resistance. This applies to all antimicrobials and applies as much today as it did in 1945.

Antimicrobial resistance can be defined as the ability of a microorganism to withstand the effects of antimicrobial treatments, including treatments to which it was susceptible in the past. While antimicrobial resistance can be attributed to the phenomenon of natural selection, each time we expose microorganisms to antimicrobials we expedite this 'survival of the fittest' mechanism – when exposed to chemicals designed to kill them; microorganisms will adapt or die. Those microorganisms which adapt or develop resistance become the prominent form and procreate, passing on their resistance. Many bacteria also have the ability to transfer genes horizontally, known as gene transfer, to neighbouring bacteria. This allows bacteria to respond to an antimicrobial attack by altering their genome to out-compete other organisms in the environment. Overuse of antimicrobials also contributes to the problem of antimicrobial resistance by profoundly disturbing the normal flora of the body, thereby promoting conditions for overgrowth of resistant bacteria.

Antimicrobials are societal drugs. That is, the use of an antimicrobial in one individual can affect others and can also affect that individual in the future. In 2014, the World Health Organisation (WHO) warned "A post-antibiotic era – in which common infections and minor injuries can kill – far from being an apocalyptic fantasy, is instead a very real possibility in the twenty-first century". Antimicrobial stewardship can be defined as a suite of interventions to limit inappropriate antimicrobial use. The aim of an antimicrobial stewardship programme is to optimise

> **"Penicillin should only be used if there is a properly diagnosed reason and, if it needs to be used, use the highest possible dose for the shortest time necessary. Otherwise antibiotic resistance will develop."**
>
> **Alexander Fleming, 1945**

Figure 2: **Consumption of Antibacterials for Systemic Use in the Community in Europe in 2018** *(Source: ECDC)*



antimicrobial selection, dosing, route and duration of therapy to maximise clinical outcome. It also aims to reduce unintended consequences such as the emergence of resistance, adverse drug events and cost. One of the most important parts of antimicrobial stewardship is that everyone has a role to play and pharmacists can contribute significantly to antimicrobial stewardship.

Approximately 80% of antimicrobials consumed in Ireland are dispensed in primary care, so it is imperative that antimicrobial stewardship is embedded in community settings. Data collected by the European Centre for Disease Control (ECDC) for 2018, placed Ireland in the upper quartile in Europe in terms of consumption of antibacterials for systemic use in the community (*Figure 2*), consuming approximately double the amount of antibacterials in the community as the Netherlands.

One of the first principles of good antimicrobial stewardship is to avoid unnecessary use of antimicrobials, e.g. against viral and self-limiting infections. Community pharmacists are well placed to offer alternatives to antimicrobials for such infections. Advising patients how to manage their symptoms while the infection resolves is key, e.g. pain/ temperature/ sinusitis/ cough/ runny nose/ minor cuts and grazes. www.undertheweather.ie is a useful website to direct patients towards for self-management of viral infections.

Right Drug

The principles of good antimicrobial stewardship encourage that antibiotic therapy should be led by microbiological culture and sensitivity where possible. This is not always possible in primary care and more often than not, antibiotics are commenced empirically. In such cases, a narrow spectrum agent is usually preferred to a broad-spectrum agent and choice should be guided by local or national guidelines. The national guidelines for treatment of infections in primary care are all published on www.antibioticprescribing.ie. Community pharmacists should be familiar with these guidelines. Where necessary, based on your clinical judgement, deviation from the current guidelines can be discussed with the prescriber. It is important for community pharmacists to be familiar with the Red/Green Initiative, which outlines the preferred antibiotics for use in primary care and those to be avoided. The Green agents are either associated with a better adverse effect profile or less potential for promoting antimicrobial resistance compared to the Red agents. However, for certain clinical scenarios, it may be appropriate to prescribe a Red agent. GPs are also familiar with this list and each quarter receive a report outlining their percentage green and percentage red prescribing. Since its introduction, we have seen a 9% increase in green prescribing nationally from 55% to 64%. Conversations with GPs about green prescribing by community pharmacists can be a welcome part of this growth.

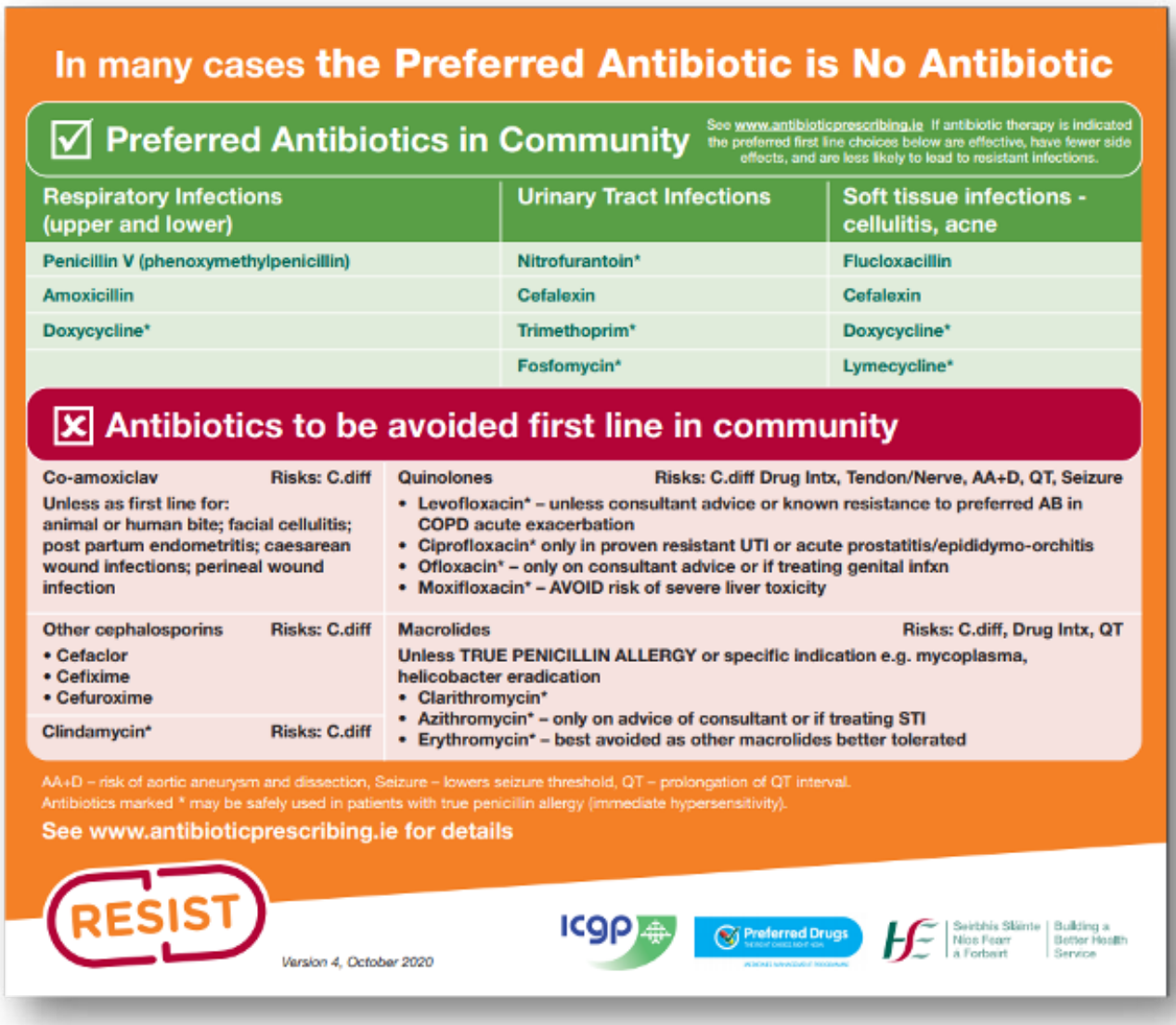
Always check the allergy status of a patient before dispensing the antibiotic. Where possible, clarify and document the nature of the allergy as this may help determine which antibiotics may be safe to use in the future. De-labelling an untrue penicillin allergy may help to ensure the most appropriate treatment is available to the patient for treatment of a serious infection in the future.

Right Dose

Sub-optimal dosing may result in under-treatment of infection, increasing the risk of repeated and prolonged course and/or development of resistance. Overtreatment results in unnecessary exposure to antimicrobials, increasing the risk of adverse drug reactions including development of *Clostridioides difficile* infection. As medication experts, through interaction with prescribers, community pharmacists can ensure that antimicrobials are prescribed at the correct dose.

Figure 3: **www.undertheweather.is is a useful website to direct patients to for self-management of viral infections**

Figure 4: **The 'Red/ Green Initiative' is a quality improvement initiative introduced to guide prescribers in primary care towards the best agents to prescribe to treat infections while limiting adverse events including resistance.** *(Source: www.antibioticprescribing.ie)*



Right Frequency

Dosing frequency is determined by the pharmacokinetics and pharmacodynamics (PK-PD) of the individual drug and their influence on rate of bacterial killing. For time-dependent agents, e.g. β-lactams (e.g. penicillins and cephalosporins), the rate of bacterial killing is maximised by increasing dose frequency. Therefore, the most important parameter for activity in time-dependent agents is time spent over the MIC. Hence, phenoxymethylpenicillin and flucloxacillin are recommended to be dosed four times a day. For concentration-dependent agents, e.g. azithromycin, the bacterial killing power increases with a greater pharmacologically relevant concentration relative to the MIC. The most important parameter in determining activity in concentration-dependent agents is the ratio of maximal drug concentration to the MIC and the ratio of 24 hours area under the plasma concentration time curve to the MIC *(Figure 5)*.

Correct frequency is also important when we consider dosing schedules. For example, a four times daily dose is ideally spread over the 24-hour clock and so should ideally be taken every 6 hours. This is important to discuss with patients to ensure that the doses are spread out as much as practically feasible throughout their waking hours.

Case Study – Right Dose

Scenario

A patient is prescribed co-amoxiclav 625mg TDS for 7 days. The patient has swallowing difficulty and needs a liquid preparation. You have Augmentin Duo® 400mg/75mg/5 mL and Augmentin Paediatric® 125mg/31.25mg/5mL suspensions in stock. Which do you dispense:

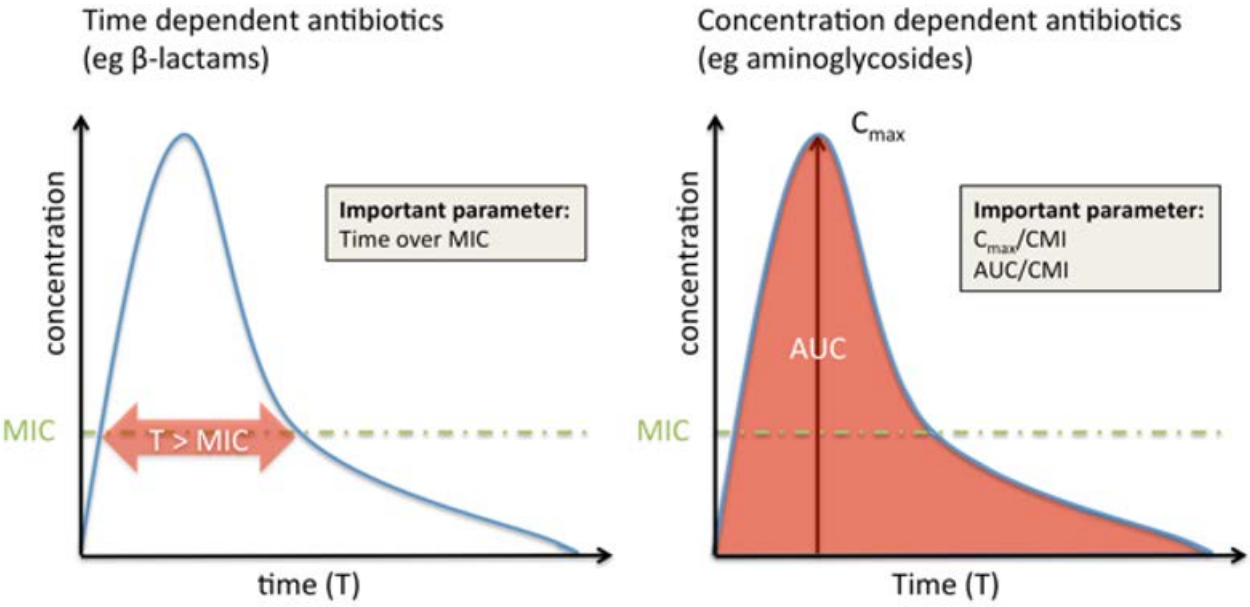
a) 6.8mL of Augmentin Duo® TDS
b) 7.5mL of Augmentin Duo® TDS
c) 20mL of Augmentin Paediatric® TDS

Answer:

Giving 6.8mL or 7.5mL of Augmentin Duo® results in giving a slight excess of amoxicillin, and more problematically, under-dosing clavulanic acid. Clavulanic acid is a β-lactamase inhibitor, broadening the spectrum of activity and so it is useful in infections where the bacteria may be resistant to amoxicillin alone.

Therefore, 20mL of Augmentin Paediatric® is the correct dose!

Figure 5: **Time-Concentration Curve identifying the important parameters for time dependent and concentration dependent antibiotics** *(Source: Antimicrobial Stewardship from Principles to Practice, British Society of Antimicrobial Chemotherapy)*



MIC: minimum inhibitory concentration
C_{max}: peak concentration
AUC: «rea under the curve

Case Study – Right Frequency

Scenario
A patient is prescribed nitrofurantoin 100mg BD for 7 days. You have Macrodantin® 100mg and MacroBid® 100mg in stock. Which do you dispense:

a) Macrodantin® 100mg
b) MacroBID® 100mg

Answer:
Macrodantin® capsules are an immediate release preparation. Nitrofurantoin has a short half-life and as such usually needs to be administered four times daily, which these immediate-release capsules are designed for.

The MacroBID® – with the BID clue in the name – is a prolonged-release preparation designed to slowly release the 100mg over 12 hours leaving no gap for the bacterial growth, thus fighting the infection for the entire 24 hours.

Therefore, the correct answer is MacroBID®. Macrodantin® should never be given twice daily.

Drug-food and drug-drug interactions

Another consideration is the effect of food or other medication on the bioavailability/adverse effect profile of the antimicrobial:

- Phenoxymethylpenicillin and flucloxacillin should be taken on an empty stomach;
- Doxycycline should be taken with a full glass of water and the patient should be advised to sit upright for 30 minutes after taking to avoid oesophagitis;
- Tetracyclines and quinolones should be dosed several hours apart from antacids and iron/ calcium / magnesium/ zinc-containing products to avoid chelation in the gut which would result in reduced systemic absorption and efficacy of antibiotic; and
- Azole antifungals and quinolones can prolong the QT interval and caution is advised with concomitant use of other QT prolongers (e.g., antipsychotics, antidepressants, domperidone, and several others).

Right Duration

The duration of antibiotic courses should be the shortest effective duration. Prolonged duration of antimicrobials is a form of antimicrobial overuse and the risk of antibiotic-related adverse events, including resistance, increases with prolonged treatment courses. Pharmacists can have a role in highlighting prolonged courses to prescribers. The recommended durations for treatments of infection in primary care are outlined on www.antibioticprescribing.ie. It is important to advise the patient to complete the prescribed course and take as directed.

In summary, community pharmacists have an important role to play in ensuring prudent and appropriate use of antimicrobials:

- ✔ Find out what the antimicrobial is prescribed for, check whether the treatment choice, dose, frequency and duration corresponds with the guidelines on www.antibioticprescribing.ie.
- ✔ Check allergy status of patient.
- ✔ Advise patient how best to take antimicrobial considering lifestyle, drug-drug/ drug-food interactions.
- ✔ Advise patient of main adverse effects and how to manage these.

CPD overview

Self-appraisal

- [ ] What do you know about antimicrobial stewardship in Primary Care?
- [ ] Am I aware of the right dose, frequency and duration for antibiotic courses?
- [ ] Am I familiar with the national guidelines for the treatment of infections in primary care?

Personal plan

Including a list of desired learning outcomes in a personal learning plan is a helpful self-analytical tool.

- [ ] Create a list of desired learning outcomes.
- [ ] How will I accomplish these learning outcomes?
- [ ] Identify resources available to achieve learning outcomes.
- [ ] Develop a realistic timeframe for the plan.

Action

Activities chosen should be outcomes based to meet learning objectives.

- [ ] Implement plan.
- [ ] Read this article on Antimicrobial Stewardship in Primary Care.
- [ ] Evaluate professional resource materials available in the pharmacy and source additional material if necessary.
- [ ] Evaluate patient support material and source additional material if necessary.

Evaluate

Consider outcomes of learning and impact of learning.

- [ ] Have I met my desired learning outcomes?
- [ ] Do I now feel confident to engage with prescribers and patients on Antimicrobial Stewardship in Primary Care?
- [ ] Provide an example(s) of changes that I have implemented in my pharmacy practice.
- [ ] Have further learning needs been identified?

Document your learning

- [ ] Create a record in my ePortfolio.
- [ ] As part of this record, complete an evaluation, noting whether learning outcomes were achieved and identifying any future learning needs.

✔ Advise patient to complete the course. If there are any tablets/ capsules/ liquids remaining, they should be returned to the pharmacy for disposal. They should not be disposed of in household waste as exposure to environment to antimicrobials will promote antimicrobial resistance.

✔ Pharmacists are well placed to advise on OTC remedies and self-management of upper respiratory tract infections. Most upper respiratory tract infections are viral and antibiotics are not needed. The website www.undertheweather.ie is a useful resource for patients.

To support antimicrobial stewardship in the community, each Community Health Organisation has an antimicrobial pharmacist. Contact details can be found on https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/about-us/.

Your 5-minute assessment

Answer the following five questions:

1. Name two ways in which bacteria can pass on their resistant genes.

2. Which of the following is NOT a recommended first line/ green agent in the community setting:
   a. Doxycycline
   b. Amoxicillin
   c. Clarithromycin
   d. Cefalexin

3. In which of the following situations may it be appropriate to empirically prescribe a macrolide?
   a. In a urinary tract infection
   b. In a patient with a true penicillin allergy
   c. In patients with a prolonged QT interval

4. Which of the following antibiotics carry a significant risk of serious adverse effects on muscle, tendons, bone and the nervous and circulatory systems:
   a. Amoxicillin
   b. Ciprofloxacin
   c. Lymecycline
   d. Trimethoprim

5. Where can the national guidelines for antibiotic prescribing in the community setting in Ireland be found?

Answers
1. Procreation and horizontal gene transfer. **2.** c (Clarithromycin).
3. c. In a patient with true penicillin allergy. **4.** c. (Ciprofloxacin).
5. www.antibioticprescribing.ie