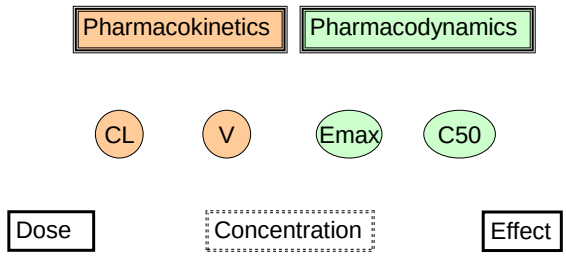
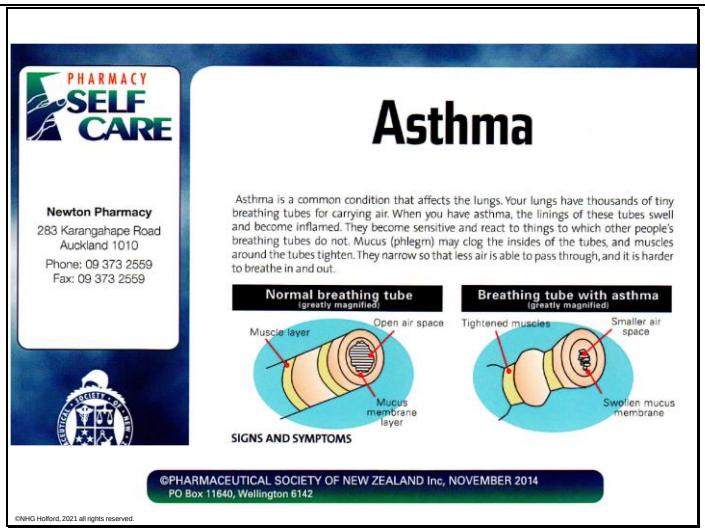
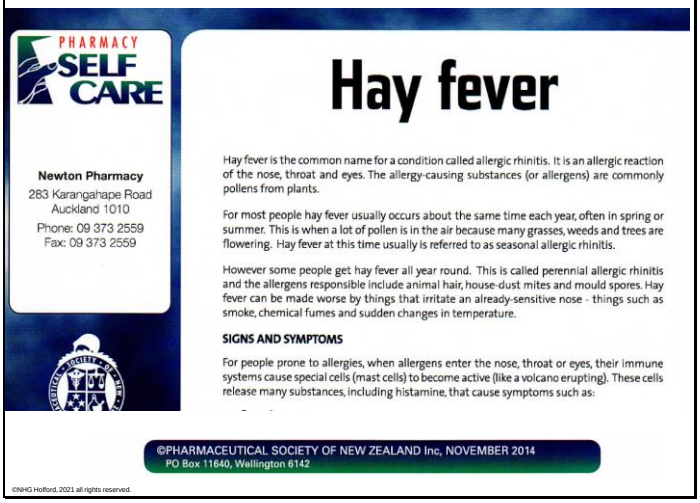
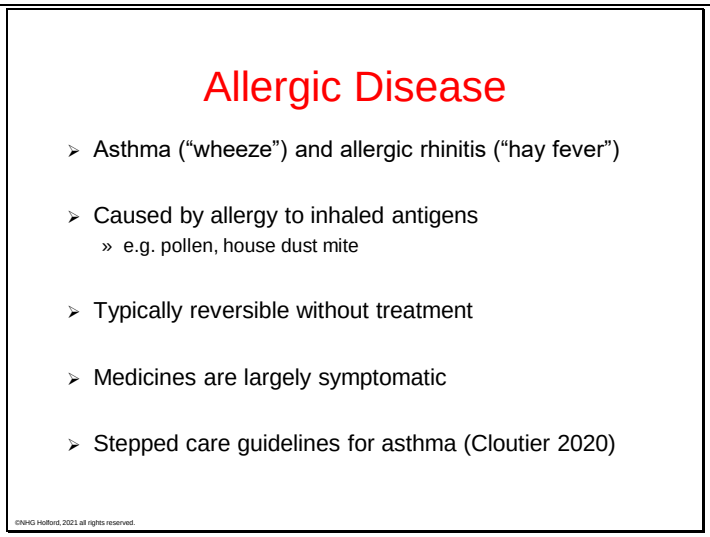
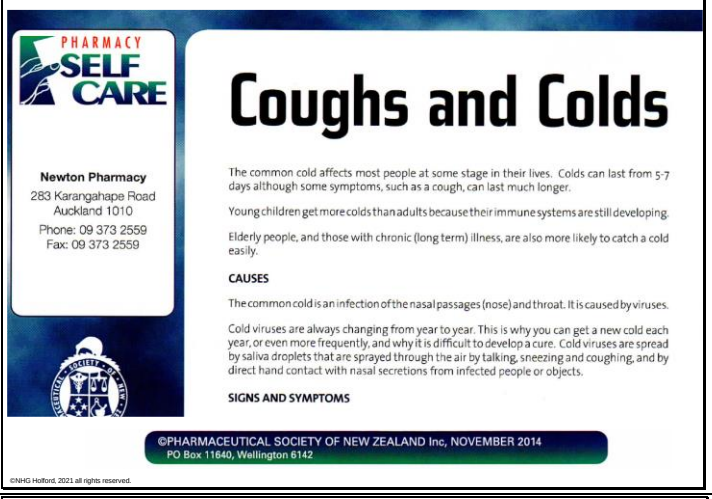
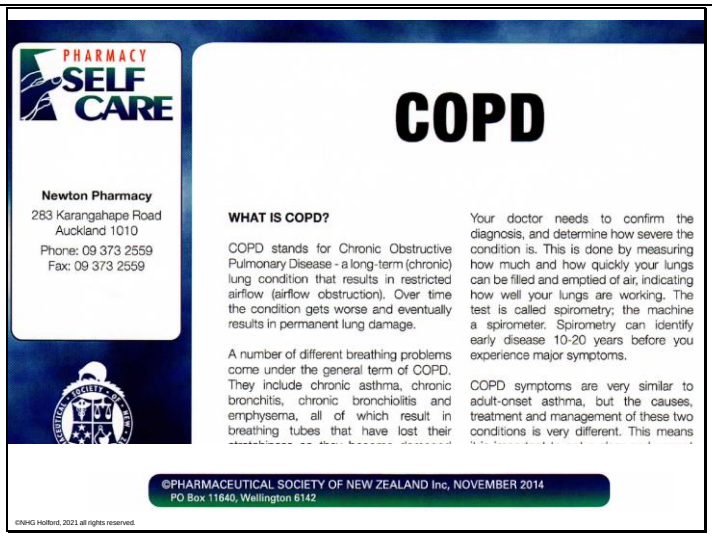
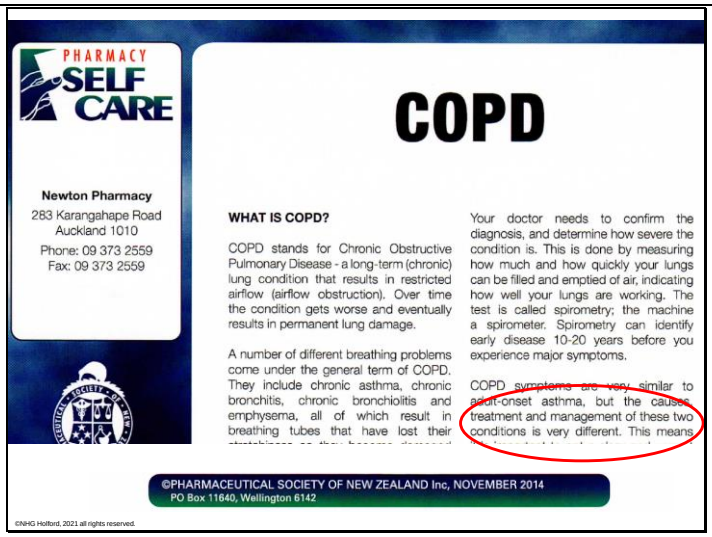
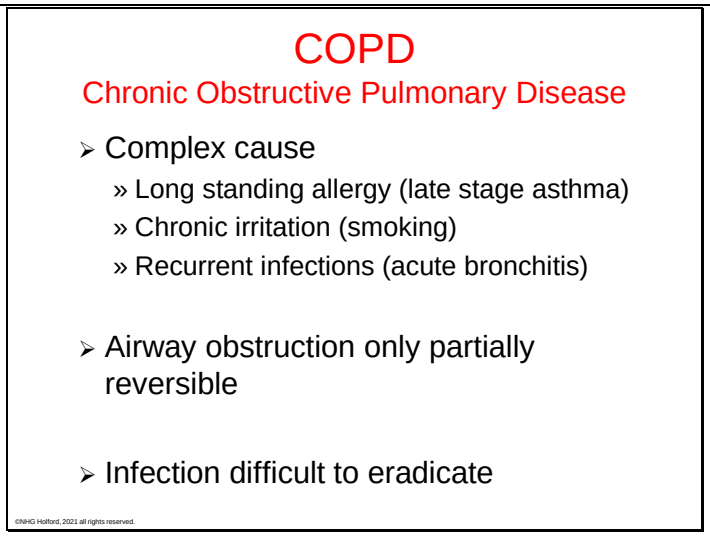
Slide 1	# Respiratory Pharmacology Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2	# Pharmacology φαρμακον pharmakon Medicine Poison Magic Spell 	Pharmacology is derived from a Greek word (pharmakon). The Greeks used this word to mean a medicine, a poison or a magic spell.
Slide 3	# Clinical Pharmacology  	Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).

Slide 4	# Respiratory Disease and Pharmacology 	
Slide 5	## Objectives ➢ Be familiar with the principal diseases of the respiratory system and the common medicines used to treat respiratory disease ➢ Learn the mechanism of action, clinical benefits and adverse effects of common medicines 	Lectures are intended to highlight main mechanisms of disease and actions of common medicines. Disease and pharmacological mechanisms can often be found on Wikipedia. Adverse effects are often complex and may relate to interaction of several medicines used at the same time. Consult MedSafe (http://www.medsafe.govt.nz/) or NZ Formulary (http://nzformulary.org/) for details.
Slide 6	## Respiratory Diseases ➢ Asthma & Allergic Rhinitis ➢ Upper respiratory tract infection (URTI) ➢ Coughs and colds ➢ Chronic Obstructive Pulmonary Disease (COPD) ➢ Cystic fibrosis 	What are the principal respiratory diseases that are treated with medicines? Malignant diseases such as lung and throat cancer and antibacterial/antiviral/antifungal treatment of respiratory tract infections are not covered in this lecture.

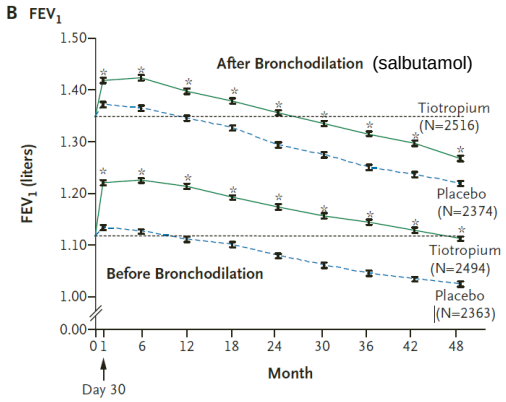
Slide 7		
Slide 8		
Slide 9		Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF, Jr, Pace W, Schatz M. Managing Asthma in Adolescents and Adults: 2020 Asthma Guideline Update From the National Asthma Education and Prevention Program. JAMA. 2020.

Slide 10	 	
Slide 11	Coughs and Colds, Sore Throats ➢ Symptoms of allergy and/or infection ➢ Usually viral infection • Choryza – the common cold • Influenza (A, B, C, D) • Covid-19 (SARS-CoV-2) • Infectious mononucleosis – glandular fever ➢ No proven place for use of medicines • Exception – Streptococcal infection 	Common symptoms. Mainly self limiting. https://en.wikipedia.org/wiki/Vitamin_C_and_the_common_cold Vitamin C use is controversial. A profitable placebo for pharmacists? Limited benefit of anti-virals (e.g. olseltamivir (Tamiflu)) in influenza. https://en.wikipedia.org/wiki/Oseltamivir "A 2014 Cochrane review concluded that oseltamivir does not reduce hospitalizations, and that there is no evidence of reduction in complications of influenza" Claims of benefit of chloroquine to treat covid19 associated pneumonia have been made (Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends. 2020;DOI: 10.5582/bst.2020.01047.) but no reports have been published describing clinical trials and results (1 March 2020). Cough cures? http://www.webmd.com/cold-and-flu/features/cough-relief-how-lose-bad-cough#1 Medicines have little objective benefit. Symptomatic remedies (steam inhalation, hot shower, whisky etc) https://en.wikipedia.org/wiki/Streptococcal_pharyngitis Penicillin to reduce risk of rheumatic fever

Slide 12		
Slide 13		Airway obstruction treatments are much the same for asthma and COPD.
Slide 14		Acute exacerbations can be difficult to distinguish from asthma and heart failure. Progressive disease. No medicines known to slow progression of obstructive features. Late stage disease may require domiciliary oxygen. Mucolytics have little objective benefit. Mainly placebo effect. https://en.wikipedia.org/wiki/Mucokinetics: “Many mucokinetic drugs are available, including Sodium citrate or Potassium citrate, Potassium iodide, Guaiphenesin, Tolu balsam, Vasaka, Ammonium chloride. Many mucolytic drugs are available, including acetylcysteine, ambroxol, carbocisteine, erdosteine, mecysteine, and dornase alfa”.

Slide 15	**Cystic Fibrosis** ➢ Genetic cause » 1 in 3000 newborns affected » CFTR - cystic fibrosis transmembrane conductance regulator protein ➢ Symptoms may start in infancy » Respiratory (frequent infections) » Intestinal (malabsorption) ➢ Lifelong management 	https://en.wikipedia.org/wiki/Cystic_fibrosis: "cystic fibrosis transmembrane conductance regulator protein (CFTR)" "CFTR is involved in production of sweat, digestive fluids, and mucus. When CFTR is not functional, secretions which are usually thin instead become thick." Many clinical teams (respiratory, gastrointestinal, nutritional, psychological). Multiple medicines. Lots of potential interactions. Challenge for everyone to stay alert to medicine interactions and adverse effects.
Slide 16	**Allergy Mechanism** ➢ Inflammation » Swelling » Itching » Liquid exudate ➢ Mediators » Mast cells » Eosinophils » Histamine » Cytokines 	
Slide 17	**Allergy Treatment** ➢ Bronchodilators (asthma, COPD) » formoterol, tiotropium » theophylline, magnesium sulphate (hospital) ➢ Anti-inflammatory steroids (asthma) » beclomethasone, prednisone, fluticasone (hay fever) ➢ Mast cell stabilizer/leukotriene receptor antagonist (asthma) » cromoglicate, montelukast ➢ Antihistamine (hay fever) » fexofenadine ➢ Vasoconstrictor (hay fever, croup) » oxymetazoline, nebulized adrenaline (pseudoephedrine, cocaine) 	NZ Formulary management of asthma (http://nzf.org.nz/nzf_1692, http://nzf.org.nz/nzf_1688) Bronchodilators are generally rapid in onset "relievers" Short acting beta agonists (SABA) are no longer recommended *Big Changes in Asthma Treatment in New Global Guidelines - Medscape - Oct 01, 2019.* Anti-inflammatory steroids are generally slow in onset "preventers" https://en.wikipedia.org/wiki/Cromoglicic_acid "cromolyn sodium. This drug prevents the release of inflammatory chemicals such as histamine from mast cells." https://en.wikipedia.org/wiki/Montelukast "it blocks the action of leukotriene D4 (and secondary ligands LTC4 and LTE4) on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction

		otherwise caused by the leukotriene and results in less inflammation." Antihistamines are not used to treat asthma because they have no effect on bronchoconstriction. Fexofenadine (non-sedating H1-histamine receptor antagonist) is effective by suppressing histamine induced acute irritation and exudation. Vasoconstrictors reduce exudate by reversing inflammatory cytokine and histamine induced vasodilatation. http://nzf.org.nz/nzf_6107 "Symptoms of nasal congestion associated with the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal mucosa. They often give rise to rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events. "
Slide 18	**Bronchodilator Mechanism** ➢ Beta2-adrenoceptor agonists » salbutamol (short acting beta agonist) » formoterol, salmeterol (long acting beta agonist; LABA) » activate beta-receptors which leads to bronchial smooth muscle relaxation ➢ Muscarinic cholinergic antagonists » iprotropium, tiotropium (LAMA) » Block acetyl choline (bronchoconstrictor) ➢ Theophylline » Adenosine receptor antagonist (like caffeine) » Phosphodiesterase inhibitor 	Long acting beta agonists (LABA) have high affinity for receptor and partition into cell membrane near receptor. Long action may due to slow dissociation from receptor and/or deport slow release from membrane to receptor. LABA NZF recommends LABAs (salmeterol, formoterol) only in combination with inhaled steroids (see NZ formulary http://nzf.org.nz/nzf_1706#nzf_1710). 2019 guidelines recommend formoterol with inhaled steroids for mild asthma https://ginasthma.org/wp-content/uploads/2019/04/GINA-2019-main-Pocket-Guide-wms.pdf Olodaterol is an ultra-long-acting β adrenoreceptor agonist (ultra-LABA) used as an inhalation for treating patients with chronic obstructive pulmonary disease (COPD), manufactured by Boehringer Ingelheim. https://en.wikipedia.org/wiki/Olodaterol LAMA=long acting muscarinic agonist

Slide 19	**COPD Progression and Treatment**  Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-Year Trial of Tiotropium in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2008;359(15):1543-54. 	The FEV1 is a measure of airway resistance. Tiotropium is an inhaled anti-cholinergic bronchodilator. FEV1 was measured before and after bronchodilatation with inhaled salbutamol (albuterol). Patients with chronic obstructive pulmonary disease (COPD) treated with placebo or with tiatropium show an initial symptomatic response which appears to be maintained in the tiatropium treated group. There is no indication of a disease modifying effect. Before bronchodilatation, the annual rates of decline were the same in the tiotropium group and the placebo group: 30±1 ml per year. After bronchodilatation, the annual rate of decline was 40±1 ml per year in the tiotropium group, as compared with 42±1 ml per year in the placebo group. Note the much bigger response to beta-agonist bronchodilator than to tiotropium. **GOLD 2017 changes direction.** *Singh D. Pharmacological treatment for COPD; Br J Clin Pharmacol. 2017;83(5):935-7.* **Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis.** *Zheng Y, Zhu J, Liu Y, Lai W, Lin C, Qiu K, et al. BMJ (Clinical research ed). 2018;363:k4388-k.* **How Does Triple Therapy Stack Up for COPD?** *David J. Amrol, MD reviewing Zheng Y et al. BMJ 2018 Nov 6 https://www.jwatch.org/na47892/2018/11/15/how-does-triple-therapy-stack-copd*
Slide 20	**Mechanism** ➢ Anti-inflammatory Steroids » Inhaled (topical) – Beclomethasone » Systemic (oral) – Prednisone (or prednisolone) ➢ Intra-cellular glucocorticoid receptor » Slow turnover of proteins which lead to release of inflammatory cytokines » Slow onset of action and persistent effect 	https://en.wikipedia.org/wiki/Glucocorticoid_receptor Prednisone has short half-life (2-4 h). Doses given once a day or event alternate days. Prednisone and prednisolone are interconvertible in the body. No real differences in the clinical pharmacology of these 2 molecules. https://en.wikipedia.org/wiki/Prednisone https://en.wikipedia.org/wiki/Prednisolone PKPD of inhaled corticosteroids http://www.atsjournals.org/doi/full/10.1513/pats.200403-025MS

Slide 21	# Theophylline Target Concentration Clin. Pharmacokinet. 25 (6): 495-505, 1993 Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L? A Randomised Concentration-Controlled Trial *Nicholas Holford*[1], *Peter Black*[1], *Ron Couch*[2], *Julia Kennedy*[3] and *Robin Briant*[1] 1 Department of Pharmacology and Clinical Pharmacology, School of Medicine, University of Auckland, Auckland, New Zealand 2 Department of Clinical Chemistry, Auckland Hospital, Auckland, New Zealand 3 Department of Pharmacy, School of Medicine, University of Otago, Dunedin, New Zealand ➢ How can a target concentration of 10 mg/L be maintained? 	A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting. If the target concentration is known what dose rate is needed to maintain the concentration at the target?
Slide 22	# Clearance *Clearance describes the relationship between <u>concentration</u> and the <u>rate of elimination</u> of drug from the body* $Rate\ Out = CL \times Concentration$ 	The definition of clearance (CL) links drug concentration to the rate of elimination (rate out). Note that elimination and clearance are NOT the same thing. Because the definition of clearance is linked directly to concentration it is important to know in what fluid the concentration is obtained. Most commonly drug clearance is based on drug concentration in plasma or serum. For all practical purposes there is no difference between plasma and serum concentrations.
Slide 23	# Maintenance Dose Rate ➢ At Steady State: $Rate\ Out = Rate\ In$ ➢ Therefore $Rate\ Out = CL \cdot Concentration$ $mg/h = L/h \cdot mg/L$ $30\ mg/h = 3\ L/h \cdot 10\ mg/L$ 	Maintenance dose rate can be predicted if the target concentration and the drug clearance are known. Steady state drug concentrations are maintained when the rate of drug administration (rate in) is equal to the rate of elimination (rate out). Using the definition of clearance we can predict the steady state rate in. Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are then readily predicted with units of mg/h.

Slide 24	**Adverse Effects** ➢ Beta agonists » Tachycardia, tremor » Arrhythmias, hypokalaemia ➢ Steroids » Acute courses – very few adverse effects » Mouth/throat infection (“thrush”) » Growth slowing (children) ➢ Theophylline » Nausea (vomiting) » Tachycardia (arrhythmias – heart, brain) 	
Slide 25	**Pulmonary Toxicity of Medicines and Poisons** ➢ Pulmonary Fibrosis » Amiodarone (anti-arrhythmic) » Nitrofurantoin (antibiotic) » [Methysergide (anti-migraine)] » Paraquat (weed killer) 	https://en.wikipedia.org/wiki/Methysergide https://en.wikipedia.org/wiki/Paraquat https://en.wikipedia.org/wiki/Pulmonary_toxicity
Slide 26	**Monitoring Treatment** ➢ Asthma » Peak Expiratory Flow Rate meter » Patient symptom diary » Theophylline target concentration intervention – NZ formulary out of date and misleading – Target is 10 mg/L (55 umol/L) – Sample in middle of dosing interval 	http://nzf.org.nz/nzf_1756 “Therapeutic drug monitoring plasma-theophylline concentration for optimum response 55–110 micromol/litre (10–20 mg/litre); measure theophylline concentration 4–6 hours after a dose (sampling times may vary—consult local guidelines), and at least 5 days after starting oral treatment, and at least 3 days after any dose adjustment” There is no point in waiting 5 days after starting treatment. Steady state is typically reached after 2 days. Blood sampling in the middle of the dosing interval is closest to steady state average conc and thus most useful for estimating clearance.

Slide 27