Can computerised clinical decision support improve antimicrobial prescribing?

Design of a simple computerised intervention to improve antibiotic prescribing in a university teaching hospital.

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Declaration

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Summary

The overuse of antibiotics and their inappropriate use has been implicated in the development of antimicrobial resistance and escalating antimicrobial acquisition costs. Controlling the use of antibiotics and promoting the rational use of antibiotics has been identified as a means of using our existing range of antibiotics effectively and cost-efficiently, while reducing the rate of development of antimicrobial resistance.

Clinical decision support (CDS) can been described as any intervention which assists in the medical decision-making process. It has found particular application in the prescribing process, to support appropriate medicines management. There are many examples of CDS in the microbiology literature.

Infection is a clinically complex and dynamic area, and the use of antibiotics can be equally complex, depending on many different environmental and clinical factors. Clinical microbiologists provide guidance on the treatment and prevention of infection at a local, national and international level, through the provision of antibiotic treatment guidelines. However, it is acknowledged that compliance with this guidance is variable and at times poor. The reasons for this are many.

This study established the rate of compliance with the local antibiotics guidelines in the area of lower respiratory tract infections (LRTIs) in a large teaching hospital. It also calculated the difference in antibiotic consumption and cost for the study patients compared to those that would have resulted, had the guidelines been followed. The overall rate of compliance was 21% and patients received fewer doses of antibiotics than would have been the case had the guidelines been followed. This was accounted for by only one of the two required antibiotics being prescribed in 14% of patients. The study also showed that the cost of antibiotics in this group was 47% higher than it should have been, due to the unnecessary use of an expensive broad-spectrum intravenous antibiotic, piperacillin / tazobactam in 14% of patients.

This study critically examined the medical literature dealing with the application of CDS in the domain of infection. Many different models and examples of CDS, both informatics-reliant and informatics-independent, were identified and evaluated. The

author chose a feasible example of a computerised CDS that could be easily implemented within existing informatics and clinical systems, as part of a broader package of interventions to improve antibiotic use. This consisted of the provision of the guidelines in an electronic interactive form. A prototype was developed and assessed for compliance with the critical factors for successful CDS.

Assessment of the effect of the study intervention on prescribing compliance rates did not form part of this dissertation. However, it is intended that the prototype be further developed into a full set of electronic guidelines as part of a complete antimicrobial stewardship programme.

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Glossary of terms

Academic detailing	Individualised client (e.g. a clinician) education
ATC	Anatomical Therapeutic Classification
ANN	Artificial Neural Network
Antibacterial drug	A drug which is active against bacteria
Antibiogram	A record showing the sensitivity of pathogens to various antimicrobial drugs
Antibiotic	A drug with activity against a living thing, generally a microbe, but the term is often used in the context of activity against bacteria
Antimicrobial drug	A drug which is active against a microbe
Bacteriaemia	Bacterial blood infection
C&S	Culture and sensitivity (to antimicrobial drugs), a test performed on biological samples
CAP	Community-acquired pneumonia
CBR	Case-based reasoning
CDC	Centre for Disease Control
CDS	Clinical Decision Support
COPD	Chronic obstructive pulmonary disease
CPG	Clinical practice guideline
CPN	Causal probability network
CPOE	Computerised Physician Order Entry
Culture	Growth of microbes from a biological sample used to identify pathogens
DDD	Defined daily dose
dm+d	Dictionary of medicines and devices
EMEA	European Medicines Evaluation Agency
EPR	Electronic patient record
EU	European Union
FDA	Food and Drugs Administration
FL	Fuzzy logic
HAP	Hospital-acquired pneumonia
HELP	Health Evaluation though Logical Processing
HIPE	Hospital Inpatient Enquiry system

HIS	Hospital information system
HIV	Human immunodeficiency virus
HL7	Health level 7
HSE	Health Services Executive (Ireland)
HTML	Hypertext mark-up language
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICT	Information and communications technology
ICU	Intensive care unit
IMB	Irish Medicines Board
Immunosuppression	Suppression of a person's immune response to infection; these patients are usually taking a medication with this effect, to treat a disorder, or they may have a disease which suppresses their immune system. Such patients are more susceptible to infection and more likely to have a more severe infection than a person with a normal immune system.
IRR	Interpretation / Retrieve / Reuse (in CBR)
IV	Intravenous
LDS	Latter Day Saints (hospital)
LIS	Laboratory information system
LOS	Length of stay, the time from admission to discharge
LRTI	Lower respiratory tract infection
Morbidity	An adverse clinical event, such as due to a disease
Mortality	Death, usually due to morbidity
MRN	Medical record number
MRSA	Methicillin-resistant *staphylococcus aureus*
NCHD	Non-consultant hospital doctor
NHS	National Health service (UK)
Nosocomial	Hospital-acquired (usually infection)
PAS	Patient administration system
Pathogen	Infecting organism which causes morbidity
PDA	Personal digital assistant
PDF	Portable document format
Pharmacodynamic	Time- and space-related behaviour of drugs in humans

Pharmacokinetic	Time-related behaviour of drugs in humans
Pneumonia	Acute infection of the lungs leading to morbidity
RCT	Randomised controlled trial
RIS	Radiology information system
ROC	Receiver Operator Curve
SARI	Strategy for Antimicrobial Resistance in Ireland
Sepsis	Bloodstream infection causing morbidity
SNOMED	Systematized Nomenclature of Human Medicine
TAM	Therapeutic Antibiotic Monitor
VAP	Ventilator-Associated Pneumonia
VRE	Vancomycin-resistant *Enterococcus*
VTM	Virtual therapeutic moiety (standard chemical drug name)
WHO	World Health Organisation
www	World-wide web

1. Chapter 1: Overview

1.1. Background

Infections occur frequently in the hospital setting. Clinicians use antimicrobial prophylaxis to prevent infection and use antimicrobial treatment when infection occurs. However, pathogens such as bacteria, viruses and fungi are dynamic and mutate rapidly, developing resistance to drugs, creating a moving target for clinicians. The presence of resistant pathogens makes treating infection more difficult as fewer antimicrobial drugs work. Resistance is associated with the overuse of these drugs, in particular those which have a broad spectrum of activity against many different types of pathogens (broad-spectrum antibiotics). This has adverse implications for the future treatment of infection.

Antimicrobial drugs and, in particular, anti-bacterial drugs are placing an increasing financial burden on hospital budgets, as resistance means that newer, more expensive agents need to be used. Effective use of antibiotics means fewer antibiotics doses per patient. Less resistance means that cheaper, older antibiotics may be continue to be effective against infective pathogens for longer. Both contribute to a reduction in the hospital's antibiotic budget.

Various strategies have been proposed to reduce the use and improve the effectiveness of anti-microbial drugs, thus reducing the rate of development of antimicrobial resistance (AMR). Most hospitals now have rules-based antibiotic guidelines and restrict certain antimicrobial drugs. In recent years, many institutions have developed computerised clinical decision support (CDS) systems to reduce the unnecessary use of these drugs and to target their use more efficiently and cost-effectively.

There are several strategies to reduce the use and improve the effectiveness of antimicrobial drugs. In the recent literature, computerised CDS has emerged as an important and effective tool for reduction of antibiotic use and expenditure.

1.2. Setting

The author is a clinical pharmacist in a 550- bed tertiary referral centre, which is also a teaching hospital. No computerised CDS is currently in use and all prescribing is paper-based.

International best practice dictates the development, dissemination and maintenance of local antimicrobial drugs guidelines in the hospital setting. This is led by the clinical microbiology team, with extensive input from other medical specialities and clinical pharmacy specialists. A clinical pharmacist is one who works directly with other healthcare professionals, in the hospital setting, to maximise individual patient benefit from medication, while minimising medication-related risks and adverse outcomes. In the author's organisation, the antimicrobial drugs usage policy is provided on paper in the hospitals medicines guide (a book which is published and distributed every 18-24 months) and through a Portable Document Format (PDF) link on the hospital intranet. Changes to the guidelines are communicated orally and in writing to all healthcare professionals, but the medicines guide book itself is not updated each time and therefore may not reflect current guidelines.

It is thought, by the departments of microbiology and pharmacy, that the rate of adherence to the antimicrobial drugs guidelines by doctors, when prescribing, is quite low: the average organisational rate of antimicrobial compliance in a 2008 study was 62% (n = 416) (Sanchez 2009). Non-compliance may be multi-factorial: doctors may be unaware of the guidelines existence; doctors may be aware of them yet choose not to consult them; or doctors may consult the guidelines and yet choose to prescribe outside them due to a poor fit with the patient's clinical picture, physician personal preference or patient pressure.

In the base hospital, it is the author's opinion that awareness of the guidelines is limited. Even when doctors are aware that there are guidelines, they may be difficult to access and time-consuming to interpret. Frequent rotation of junior doctors, every 3, 6, 9 or 12 months, compounds this difficulty. Antimicrobial guidelines need to be easily accessible, fast to use and easy to interpret. As the local antimicrobial guidelines are paper-based, it is not possible to know how often the guidelines are used or whether they are being deliberately over-ridden. Assessing compliance rates is onerous and time-consuming,

particularly for patients with multiple co-morbidities or an unclear focus of infection. Deliberate non-compliance with the guidelines is exacerbated by the Irish tradition of medical autonomy, particularly at consultant level. Doctors may be inclined to prescribe outside the guidelines due to time constraints, personal experience, peer pressure, pressure from other clinical staff or even from patients.

As a first stage, it seems appropriate to try to improve physician awareness and uptake of the guidelines. The author proposes to provide the guidelines in a more accessible, approachable and interactive electronic form, which may increase awareness and improve antimicrobial compliance, thereby reducing antimicrobial resistance rates, improving patient outcomes and reducing the antimicrobial drugs annual spend.

1.3. Research question

The research question is two-fold:

> Question 1. Can computerised CDS improve the rate of medical compliance with antimicrobial prescribing guidelines in general, and in what form?
>
> Question 2. Could the rate of compliance with the base hospital antimicrobial drugs guidelines, be improved by applying the principles of computerised CDS, in order to provide users with a more accessible, approachable and interactive version of the current antimicrobial drugs guidelines?

1.4. Research method

Question 1 was answered using the evidence from the literature. This project intends to examine the background to CDS for the diagnosis and treatment of infections in the hospital setting, concentrating on computerised CDS. The models and methods used will be described and, if research was performed, the results will be summarised. The literature describing the critical success factors for computerised CDS will also be described.

Question 2 was addressed by performing a "what-if" analysis, to estimate the improvement in antimicrobial prescribing if the guidelines were fully followed. As part of

this, a computerised guideline was designed with the aim of facilitating access to the up-to-date guidelines, by prescribers. A "what-if" analysis was chosen because a "before and after" experiment and a controlled trial are beyond the scope of this project. This "what-if" analysis involved:

- collection of patient data in a specified population in order to estimate the current rate of adherence to the guidelines
- quantitative measurement of antibiotic use for this population, using a universally-accepted standard unit of measurement
- calculation of estimated antibiotic use for this population, if the guidelines had been fully followed, (the "if" element of the "what–if" scenario)
- design and development of a practical computerised CDS prototype, based on the most appropriate models from the literature, but within the limitations of the author's circumstances
- testing of the prototype to ensure that the recommendations are accurate
- assessment of this prototype against those critical success factors identified in the literature in Question 1 above.

The dissertation will also discuss how, in the light of this research, the hospital might bring CDS for antimicrobial prescribing forward to the next stage.

1.5. Projected outcome

The literature is likely to suggest that the most appropriate CDS model is multi-modal with three features

(a) a Bayesian network for prediction of likely pathogens
(b) Bayesian-based antibiograms based on real laboratory culture results to predict pathogen sensitivity to antibiotics
(c) a decision-tree guideline to suggest which antibiotics should be used.

However, developing a prototype using (a) or (b) is beyond the scope of this project, although the literature will be discussed in depth in Chapter 3. The practical research element of this project will focus on (c).

1.6. What is already known on this topic

There are many actual examples of CDS to support the use of antimicrobial drugs in the literature. These vary from the very simple, such as provision of paper guidelines, to the very complex, featuring integrated microbiology, biochemistry, electronic prescribing and pharmacy information systems, working together with clinicians, to identify and appropriately treat infection, whilst minimising risk to the patient.

1.7. Contributions of this research

This study will add knowledge of how a practical, electronic form of CDS may improve the rate of prescriber compliance with antimicrobial guidelines in the author's hospital.

1.8 Overview of the dissertation

Chapter 2 describes why it is important to provide CDS for the use of antibiotics and discusses how and when CDS can be applied in this setting. Chapter 3 describes CDS interventions in the domain of infection that have been published in the medical literature and critically evaluates this literature. Chapter 4 gives details of the methods used in the author's research and chapter 5, the results. Chapter 6 discusses these results and places them in the context of the literature. It then goes on to describe how the CDS intervention can be developed in the future in the author's hospital. Chapter 7 concludes this dissertation.

2. Chapter 2: Background

Overview of Chapter 2

This chapter discusses how infective organisms (pathogens) are identified and treated, what is meant by the development of anti-microbial resistance and how to reduce it, the processes underlying the prescribing of antimicrobial drugs and initiatives to combat antimicrobial resistance. It goes on to describe how CDS can be applied in the identification of infective organisms and the treatment of infection. There is a short description of how to measure antibiotic drug consumption and the chapter concludes with a discussion of the critical success factors for computerised CDS.

2.1. Clinical background

Section 2.1 will describe how infective organisms can be identified and appropriate treatment recommendations made. It will discuss the meaning of an antibiotics spectrum of activity and describe how resistance to antibiotics develops among microbes. Factors contributing to the inappropriate prescribing of antibiotics are explained.

2.1.1. A short description of the identification of infective organisms and the treatment of infection

In the hospital environment, about one in three patients will receive antibiotics, either to treat an infection or to prevent an infection occurring, if there are risk factors, such as a surgical procedure. This latter strategy is known as antibiotic prophylaxis.

Infections are primarily caused by bacteria, but may also be due to fungi, viruses or parasites. They are described as having a *focus*. For example, this may be in the lungs (lower respiratory tract infection or LRTI), in the blood (septicaemia), in the brain (meningitis) or urinary tract; there may be multiple foci. The pathogens may be normally present in the body, but may have invaded an area where they are not normally found, causing an infection, or the pathogens may have been acquired from outside the body, such as from another person or animal, from the air or from contact with a surface. Infections may be due to multiple pathogens, or a single one. Patients in hospital tend to

be more debilitated and often have a reduced ability to fight infection. This is especially true of patients with certain types of malignancy, elderly patients, patients with multiple diseases and immunosuppressed patients. Untreated infection can be fatal. As a result, it is important to treat infection where appropriate, and to prevent infection where there is a risk.

When a patient shows symptoms of an infection, it is usual to identify the focus of the infection, to establish the likely infective organism(s), and, if treatment is warranted, to prescribe antibiotics that are likely to be active against them. Many infections require no treatment, for example, upper respiratory tract viral infections, such as the common cold; other infections may be self-limiting, for example, ear infections, where antibiotics do not improve outcomes and are therefore not indicated. The decision to treat with an antibiotic depends on the nature of the infection, the severity of the infection, whether or not it will respond to treatment, and whether or not the patient will suffer morbidity or even mortality as a result of the infection.

Once a decision has been made that antibiotics are required, the prescriber must choose one or more agents which are likely to be active against the suspected pathogens. They must also choose an appropriate dose and duration, and establish that the patient has no allergies to the drugs. In the hospital setting, it is common to culture a biological sample from the suspected infection source to see if organisms grow (culture and sensitivity – C&S). Microbial colonies can be tested against a range of antibiotics to establish their sensitivity to treatment. The result (pathogen +/- sensitivity) may then further direct antibiotic therapy, depending on whether the cultured pathogen is the same as that suspected, and how sensitive it is to the prescribed antibiotic: if resistant, the antibiotic may need to be changed; or a more narrow-spectrum antibiotic may be appropriate. This is known as streamlining or de-escalation. The whole process is summarised in Figure 1.

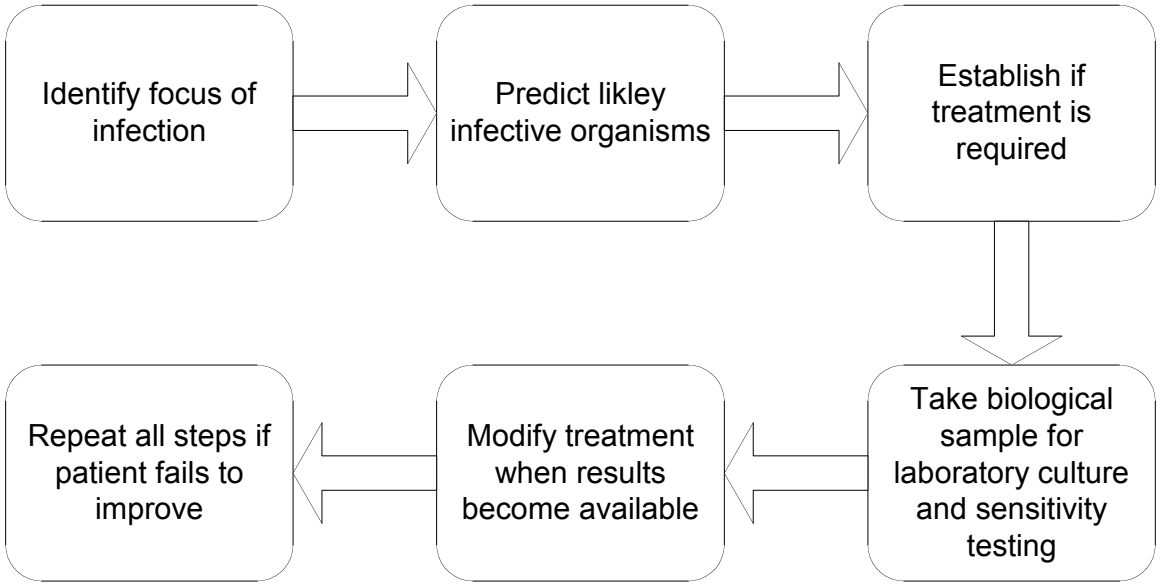

Figure 1: Identification and treatment of infection.

2.1.2. Spectrum of an antibiotic

There are several different classes of each type of pathogen, for example, bacteria can be described as Gram positive, Gram negative, aerobic or anaerobic. Within these classes, there are sub-categories. Because the number of different pathogens is high, a wide range of antimicrobial drugs is required to treat these infections. Some agents are active against many different types of pathogens (broad-spectrum) and some only against a small range (narrow-spectrum). The range or spectrum of pathogens sensitive to an antibiotic will depend on its mode of action and the ability of the bacteria to overcome this. For example, S*taphylococcus aureus* is usually susceptible to penicillins, but a mutated form, methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to penicillins, as it produces an enzyme that renders these antibiotics ineffective.

2.1.3. Development of resistance and its implications

Pathogens acquire resistance through mutation as they reproduce, and they reproduce at enormous speed and to enormous numbers. A patient infected with hepatitis C virus can have over 10^6 copies per millilitre of blood. Urinary tract infections are considered significant if there are more than 10^5 bacteria per millilitre of urine. Pathogens become resistant to antibiotics as they are exposed to them, especially at low levels. Sometimes resistance can be transferred from one pathogen to another, leading to exponential growth

of resistance in an infective organism. Resistant pathogens can also be transmitted from one person to another, or via surface, air or water transmission (Paterson 2006).

There are several principles when using antibiotics to reduce the development of resistance:

- limit exposure of pathogens to antibiotics by using them only when necessary
- treat as early as possible when indicated, before infection becomes deep-seated or before the patient becomes acutely unwell, as this can pre-dispose to further infection or other co-morbidities (Deresinski 2007)
- use targeted antibiotics by identifying the likely pathogens and using antibiotics which are active against them (Deresinski 2007)
- when the pathogen is identified, modify therapy accordingly to more narrow-spectrum antibiotics (de-escalating) (Deresinski 2007)
- when the pathogen's drug sensitivity is identified, further modify therapy (Deresinski 2007)
- use an appropriately high dose, so the pathogen is killed, not just attenuated; adjust doses using pharmacokinetic and pharmaco-dynamic parameters if appropriate
- treat for an appropriate period, so that the infection is fully cleared, before the treatment is stopped
- when using antibiotic prophylaxis for surgery, ensure that the appropriate antibiotic is given within the effective window of 2 hours of surgery: inappropriate timing can result in a 2 to 6-fold increase in the rate of surgical site infections (Burke 2001)
- practice good infection control to reduce transmission of infective organisms.

As pathogens become resistant to antibiotics, the range of treatment options available to clinicians shrinks. Common infections, occurring in the present time, are due to MRSA, vancomycin resistant *Enterococcus* (VRE), resistant K*lebsiella* or resistant *Pseudomonas aeruginosa.* Hospital-acquired infection with *Clostridium difficile* and *Norovirus* are increasingly common. Certain pathogens are more likely to be acquired in hospital (nosocomial infections) or cause an infection control problem in healthcare institutions. Much of our population is colonised with nasal / skin MRSA: the clinical problem arises when MRSA infects wounds after surgery, or enters the circulation, for example, through the use of intravenous (IV) lines used to deliver medications or nutrition directly into the

blood, especially where patients are acutely ill and less able to mount an effective immune response. In addition, new antibiotics are slow to be developed by pharmaceutical manufacturers, and tend to be very expensive. The financial burden of anti-infective agents for the author's tertiary care hospital is in the order of 50% of the total drugs budget.

In summary, appropriate use of antibiotics helps to minimise pathogen resistance and makes their use more effective. Patient mortality, morbidity and consequently, their length of hospital stay are reduced, reducing hospital costs per patient. With less resistance, the range of available treatment options available to clinicians is improved. More efficient use of antibiotics also reduces direct antibiotics acquisition costs.

2.1.4. *Factors pre-disposing to inappropriate prescribing of antibiotics*

Prescribing is a complex psychological process and many factors leading to inappropriate antibiotic use can be identified.

(a) Antibiotic guidelines tailored to local prevalence and resistance patterns may not be available, widely disseminated or regularly updated (Ebert 2007).
(b) Prescribing may be perceived as secondary to the role of diagnosis and clinicians tend to prescribe a narrow range of medications within their speciality. Physicians are not antibiotic experts and may lack the knowledge of microbiologists and pharmacists. They may prefer antibiotics with which they are familiar and which they always prescribe, regardless of local guidelines. Antibiotics with over-lapping spectra of bacterial activity may be prescribed.
(c) Prescribers may believe that newer antibiotics are "better".
(d) Physicians may not be aware of which are the likely causative organisms and therefore prescribe very broad-spectrum antibiotics unnecessarily. Even when laboratory results are available, they may be unwilling to switch to narrower spectrum antibiotics (de-escalation), in case the patient is harbouring bacteria that might not be susceptible to the narrow spectrum antibiotic.
(e) The choice of antibiotic may be appropriate, but therapy may be continued for too long, or not long enough, or at a sub-therapeutic or toxic dose. Doses may not be adjusted for changing kidney and liver function due to a lack of knowledge or fear of under-dosing.

(f) The physician may not perform laboratory analyses, follow them up, or act on the result: this is particularly true of the out-patient department (Ebert 2007). Timing is critical: biological samples must be taken before antibiotics are administered, for the results to be valid. This may not be the case, especially in an emergency, such as suspected meningitis.

(g) Antibiotics rarely cause harm and may be prescribed "just in case", particularly if a patient's symptoms *may* be due to an infection (e.g. elevated temperature). Physicians may forget to stop antibiotics if the symptoms turn out not to be due to an infection.

(h) There is an inherent fear of under-treating the patient or causing a possible re-admission with complications, if a supposed infection is not treated on first presentation; this may be associated with a risk of litigation (Ebert 2007).

(i) Surgical patients' prophylactic antibiotics need to be timed carefully in relation to the exact start time of surgery, blood loss during surgery and the duration of surgery: in a busy hospital, this may prove difficult to coordinate (Burke 2001). In many cases, prophylaxis may not even be required.

(j) In the community in particular, patients, having invested resources in a visit to the doctor, may expect an antibiotic: sometimes it is easier to prescribe one than stand by one's principles and refuse to do so. Parents worried about babies and small children may be unwilling to accept medical advice that antibiotics are not appropriate.

(k) Physicians tend not to be aware of the high cost of many antibiotics.

(l) Pressure of time and work practices means that routine reviews of antibiotics may not be considered to be urgent, unless the patient is clinically unwell. In the hospital setting in Ireland, senior surgeons rarely review the drug chart: this is left up to junior doctors who lack the knowledge and seniority to perform antibiotic review or request a microbiology consultation. Excessively long courses of prophylactic antibiotics are common.

2.2. Institutional approaches

Hospitals have responded by appointing infectious diseases clinicians and other healthcare professionals, to bridge the gap between the microbiology laboratory and the clinician. Such healthcare workers engage in antibiotic stewardship. Infection is a complex and dynamic area. The knowledge base required to work effectively and

efficiently is large and complex. In the community however, such expertise may not be available.

Microbiology specialists need to develop close working relationships with other medical disciplines and be directly involved in individual patients' clinical care. In some institutions, microbiologists work closely with clinicians and pharmacists in high risk or complex areas such as intensive care units (ICUs), oncology / haematology units and transplant units. This direct care can be facilitated though the hospital information system and electronic health record.

2.3. International approaches

The European Union (EU) and the World Health Organisation (WHO) both recognise the importance of combating the development of resistance. The EU is targeting the rise in resistance through support of research in their 7th Framework Programme. This includes research on resistance mechanism, development of point of care testing for pathogens and mapping the spread of pathogens, their phenotypes and resistance across Europe. They also promote antibiotic awareness through an annual awareness day (EU 7th Framework Programme 2009).

Antibiotic resistance is also a focus of WHO activity. Their publications relate the rise in resistance to a number of factors, including overuse of antibiotics, poor selection of agents to treat infection, unrealistic patient expectations, non-compliance with treatment leading to low level exposure of pathogens to antibiotics, cross infection in the hospital setting, increased use in veterinary medicine and physician expectations that newer agents are superior to older drugs. The WHO also provides institutions with software to monitor resistance and share information nationally (WHO 2009).

The Centre for Disease Control (CDC), based in the USA, has developed a 12 step / 4 core strategy to reduce resistance (Center for Disease Control 2009). Those in italics are amenable to computerised CDS.

- Prevent infection
  (a) vaccinate

(b) get the catheters out (a catheter is a tube or line used to deliver drugs and fluids directly into the patient's bloodstream, and which breaks the integrity of the skin – the skin is the natural barrier protecting against invasion of pathogens into the bloodstream and tissues.).

- Diagnose and treat infection
  (c) target the pathogen
  (d) access the (infectious diseases) experts
  (e) *use antimicrobial drugs wisely.*
- Practice antimicrobial control
  (f) use local data
  (g) treat infection, not contamination
  (h) treat infection, not colonisation
  (i) know when to say no to vancomycin
  (j) *stop antimicrobial treatment (when appropriate).*
- Prevent transmission
  a. isolate the pathogen
  b. break the chain of contagion.

The EU and the WHO also promote the development of new antibiotic agents through research. Currently, antimicrobial drugs are the poor relative of pharmaceuticals and do not provide a steady, long-term income stream for pharmaceutical companies, due to the temporary nature of their use and the likelihood that resistance will eventually develop. There has been only a handful of new antimicrobial drugs in the last 10 years and only two new classes of antibacterial drugs have emerged (Norrby *et al.* 2005). These drugs also tend to have a high acquisition cost, to allow pharmaceutical companies to quickly recoup their research and development costs, in spite of fast-track licensing by the Food and Drugs Administration (FDA). As a result, it is important to maintain the activity of existing antimicrobial drugs, while trying to reduce the rate of development of antimicrobial resistance.

2.4. Clinical decision support (CDS) and its role in improving the use of antibiotics

Section 2.4 describes how CDS has been applied in the domain of infection, discussing different types of intervention singly.

CDS has been defined as "any electronic or non-electronic system designed to aid directly in clinical decision-making, that uses characteristics of individual patients to generate patient-specific assessments or recommendations that are subsequently presented to clinicians for consideration" (Hunt *et al*. 1998). It has also been described as "providing clinicians or patients with clinical knowledge and patient-related information, intelligently filtered and presented at appropriate times, to enhance patient care", although this definition omits other healthcare professionals (Teich *et al*. 2005). Thurskey (2006) describes computerised decision support as "access to knowledge stored electronically to aid patients, carers and service providers in making decisions on healthcare". Computerised CDS "bridges the knowledge-performance gap" by presenting information to the user, allowing a more-informed decision to be made (Thursky 2006). CDS may be passive (non-patient specific, for example, guideline provision) or active (directly integrated into patient care).

Sintchenko (2008) has described a decision support tool-kit for antibiotic prescribing, where the clinical information system and the Laboratory Information System (LIS) interact with each other and within a series of different supports that can be classified as either assessment and monitoring tools or prescribing tools. Assessment tools include laboratory results, such as microbiology results; prescribing tools include embedded prescribing guidelines, prevalence data, Computerised Physician Order Entry (CPOE or electronic prescribing) alerts and alarms. These interact to provide decision support at the point of care.

Healthcare professionals intervene in many ways to improve the diagnosis of infection and the use of antibiotics. These are listed and then described below. CDS, including computerised CDS, can be applied to all of the interventions described.

i. *Correct identification of the likely pathogens*

ii. *targeting antibiotics to the pathogen based on laboratory results*

iii. *developing antibiotics guidelines*

iv. *antibiotic prescription surveillance*

v. *antibiotics restriction / approval programmes*

vi. *identification of redundant antibiotics*

vii. *pharmaco-dynamic modelling*

viii. *reducing IV antibiotic use through an early switch to the oral route*

ix. *clinician education and feedback on prescribing patterns*

x. *antibiotic stewardship.*

2.4.1. *Correct identification of the likely pathogens*

This first key step is to identify the likely pathogen; this will be principally determined by the infection focus. For example, urinary tract infections are commonly caused by *E. coli;* skin, soft tissue / joint infections are usually due to Gram positive organisms, such as *Staphylococcus* species; severe sore throats are often due to *Streptococcus* species. However infection is extremely dynamic and there are hundreds of different potential pathogens, complicated by a multitude of other clinical parameters; and the rules constantly change, making pathogen identification and treatment of infection dynamic and challenging

In the hospital setting, the laboratory information generated through test results is a tremendous data resource. It can be used to identify and map pathogens from specific sources of infection, to establish their sensitivity to antibiotics and to generate antibiograms (pathogen / drug sensitivity tables). As new data is incorporated in to the knowledge base, it grows and learns. As the amount of data increases, the validity of the model is likely to increase.

Artificial neural networks (ANN) are a form of learning knowledge base that use variable weights applied to parameters to model a clinical system. They are useful in mapping non-linear data, which makes them suitable for clinical systems (Frize *et al*. 2001).

The different probabilities of occurrence of different pathogen for each infection source can also be mapped in the form of a Bayesian network. Causal probability networks (CPNs) are a form of Bayesian network that establish causal relationships and assign conditional probabilities (Leibovici *et al*. 2007). CPNs allow the application of both qualitative (knowledge, expert experience and opinion) and quantitative information (data) from patient histories to a knowledge base (Andreassen *et al*. 1999).

The advantage of Bayesian and neural networks in infection is that the knowledge base can be constantly or periodically updated using real laboratory results, and therefore reflect what is actually occurring in clinical areas. This is particularly useful in such a dynamic clinical field, especially during outbreaks of either nosocomial or unusual infections. They require less data than linear statistical knowledge bases to demonstrate validity and several causal parameters can be applied simultaneously (Leibovici *et al.* 2007).

2.4.2. Targeting antibiotics to the pathogen based on laboratory results

In general, antibiotic therapy needs to be targeted to the lowest level antibiotic to which a pathogen is sensitive. This is achieved through using older and / or narrow-spectrum antibiotics, so that resistance is less likely to develop.

Targeting antibiotics occurs at three stages:

(a) when empirical treatment is chosen, based on likely pathogens (day 1)
(b) when a pathogen is cultured from a biological sample (day 2-3)
(c) when that pathogen's antibiotic sensitivity is established. (day 3-5)

Before culture results become available, antibiotics need to be targeted to the most likely infective organisms. This is called empirical therapy. The use of broad-spectrum agents may be required in this scenario, until the culture results become available. At this second stage, treatment options may be narrowed, when the pathogen or pathogen type is identified (stage 2). Treatment may be further modified when antibiotic sensitivity results are available (stage 3). This process is known as streamlining or de-escalation.

Choice of antibiotics may be integrated into CPOE at any of these stages, through the use of treatment recommendations or actionable orders sets, which can include pre-defined

prescriptions as well as electronic requests for laboratory tests, such as C&S. There is a further role for CDS here through communication of culture results to the physician and advice about changing antibiotics at stages 2 and 3 above. The process could be integrated into CPOE, where the recommended antibiotics appear as an order set for approval, and unnecessary antibiotics are selected for discontinuation. Buising *et al*, (2005) in a study of 303 samples in 108 patients, found that 30.8% of culture results indicated that the empirical antibiotics were insufficient. Furthermore, at stages 2 and 3 above, recommendations were not being implemented in up to 30% of samples based on sensitivity results, indicating a potential for CDS in this area. Alerts to optimise de-escalation of antibiotics need to be designed to improve their effectiveness.

Antibiotic recommendations may be made using Bayesian inference in different ways:

(a) Prognosis modelling

The Bayesian network can be used to predict the patient's prognosis according to the clinical management. Survival rates using particular treatments (or even no treatment) may be predicted, and this may be used to guide the optimal antibiotic therapy. The knowledge required to perform prognosis modelling is very onerous as it includes individual patient information that is not readily available in a standard or electronic form (Andreassen *et al.* 1999).

(b) Modelling the probability of pathogen sensitivity

Pathogen sensitivity patterns are used to construct antibiograms, which map pathogens to antibiotics. Sensitivity probabilities can be applied to these data, by using historical laboratory results. Because they are based on real, historical data, antibiograms will be dynamic and up-to-date.

Alternatively, treatment recommendations may be made by the application of knowledge-based rules, using Boolean or fuzzy logic. This is more common. The advantage of Bayesian networks over Boolean or fuzzy logic, in making treatment recommendations, is that the outputs are constantly updated depending on real laboratory results. This is particularly useful in the treatment of outbreaks of infection or where a specific pattern of resistance is prevalent.

2.4.3. *Antibiotics guidelines*

(a) Development and maintenance

The oldest form of CDS in the area of infection is the use of guidelines for pathogen identification and treatment recommendations. This comes under the remit of antibiotic stewardship, where infection specialists (clinical microbiologists, scientific microbiologists, clinical pharmacists specialising in infection) map infection foci to the prevalent pathogens and the antibiotics to which they are likely to be sensitive. Guidelines may be produced at a national, regional or institutional level, with specificity increasing as the geographical range decreases, as the prevalence of pathogens and their resistance patterns are geographically variable.

Developing guidelines for the empirical treatment of infection and prophylaxis of infection can help clinicians to choose the most appropriate treatment for their patient. They have the advantage of being applicable independently of information technology, for example, using paper. In general, paper guidelines are based on decisions or rules. The process is as follows:

- identify the likely infection source based on clinical symptoms
- identify the most likely pathogen(s)
- use the narrowest-spectrum antibiotics to which the pathogen(s) are likely to be sensitive; more than one drug may be needed
- perform a C&S test.

Guidelines need to be dynamic, responding quickly to the changing prevalence of pathogens and their resistance patterns. They need to be comprehensive and clinically meaningful. Microbiologists need to update their guidelines with real data from their laboratory information system on a regular basis. Guidelines also need to be updated in accordance with recommendations produced by statutory organisations, such as the Irish Medicines Board (IMB), who are responsible for medicines use and medicines safety in Ireland, or in accordance with the latest published professional consensus guidelines.

(b) Computerised guidelines

Existing paper antibiotics guidelines can be made available electronically in PDF, Hypertext mark-up language (HTML) form or integrated into a simple computerised CDS, using a rule base. Provision could be though computer terminals, a Personal Digital Assistant (PDA) or other wireless devices. They can be hosted using the organisations intranet or the world-wide web.

(c) Incorporation of guidelines into electronic prescribing systems

Electronic prescribing or CPOE is amenable to the direct provision of decision support to the physician at the point of prescribing (also known as ordering in American systems). Prescriptions for all drugs have five required fields: drug, dose, route, frequency and duration. This leads to five areas in which antibiotic prescriptions can be non-compliant with guidelines. Using the wrong antibiotic or using less than the recommended values for any of the three numerical fields (dose, frequency or duration) can lead to non-resolution of infection and a need to use newer, often more expensive antibiotics. Historically, this has been a problem with the treatment of community-acquired pneumonia (CAP): patients do not improve and subsequently present to the Emergency Department, despite treatment with the correct antibiotic, and require more intensive treatment with newer antibiotics. Prescribing the correct antibiotic, but at a dose that is too low, can also promote pathogen resistance as pathogens are exposed to low levels of drug, without being killed: this is typically the environment in which bacteria acquire resistance. Conversely, using excessive amounts of antibiotics for excessively long periods can result in opportunistic infection by other bacteria as well as unwanted side-effects for the patient, which may be serious and / or debilitating, on occasion necessitating hospitalisation.

Guidelines should therefore always specify values for all five fields of the prescription. In CPOE, these five fields are normally mandatory. A default normal, maximum and minimum dose, frequency and duration is easy to apply to CPOE and is already available in many off-the shelf systems. This can reduce the risk of error in this area.

Guidelines can be incorporated into CPOE directly through the provision of complete order sets, including C&S testing of biological samples, automatic choice of drug(s) with

standard dose, frequency and duration, and automatic biochemistry test order communications. CPOE also facilitates antibiotic restriction and approval requirements.

(d) Adherence to guidelines

Although most hospitals have antibiotics guidelines, the rate of adherence is variable, and antibiotics may not be used in the most effective or most appropriate manner. Guidelines in the community tend to be less well-defined, and under-dosing is a significant problem (Flanders & Halm 2004). This leads to the possibility of emerging resistance and opportunistic infection. There are strategies to overcome poor adherence to guidelines, at both hospital and community level, such as:

- clinician education about the importance of adhering to the guidelines
- making the guidelines simple and fast to use
- ensuring the guidelines are readily available at the point of prescribing.

2.4.4. Antibiotic prescription surveillance

The aim of surveillance is to ensure that clinicians prescribe an appropriate drug, dose, frequency, route and duration, through prescription monitoring by clinical microbiologists and clinical antibiotics pharmacists, who then make recommendations about antibiotic use to the clinician. This may be done manually through daily prescription review or it can be performed electronically, most easily through CPOE, where all active prescriptions are available for reporting and potentially, for approval. Some US and many Irish private hospitals can also do this through pharmacy ICT system surveillance, as all medications are recorded for supply and payment purposes.

2.4.5. Antibiotics restriction / approval / cycling programmes

Certain antibiotics may be restricted unless approved directly by a microbiologist or other authorised person. Unless approved, the antibiotic will not be made available for use. Approval may operate either manually, electronically through a notification system, or it may be integrated into CPOE. Restriction of antibiotics in CPOE may be achieved by suggesting more appropriate agents during the electronic prescribing process. CPOE systems may allow drugs to be restricted for prescribing at different levels of seniority. If a restricted drug is accessed, the CDS may suggest an approved alternative, or require a higher-level user authorisation before proceeding. Antibiotic cycling (the cycling of

antibiotics for the same set of pathogens for fixed time periods such as one month) is difficult to coordinate manually in practice, but CPOE has the potential to automate antibiotic choice if cycling is practiced, through automatic restriction of antibiotics in their "off" period and suggestion of the "on" antibiotic instead (MacDougall & Polk 2005).

2.4.6. Identification of redundant antibiotics

When the spectrum of antimicrobial activity of a prescribed antibiotic is more than covered by a second agent, this creates a "redundant" or unnecessary antibiotic. It is similar to the principle of "therapeutic duplication" used in CPOE, where the clinician is alerted if two drugs with exactly the same reason for use are prescribed. Surveillance can identify redundant antibiotics or the process can be automated. The identification of a redundant antibiotic is more complex than simple therapeutic duplication, due to the multiple anti-bacterial activity of each antibiotic. However, computerised CDS can readily identify them through the use of antibiograms, models that map the spectra of pathogen sensitivity to antibiotics. This is illustrated in figure 2. An American study of patients who received more than one antibiotic concurrently found that 71% of patients were receiving at least one redundant antibiotic. The pharmacy was able to identify this through automatic computerised surveillance (Glowacki *et al*. 2003).

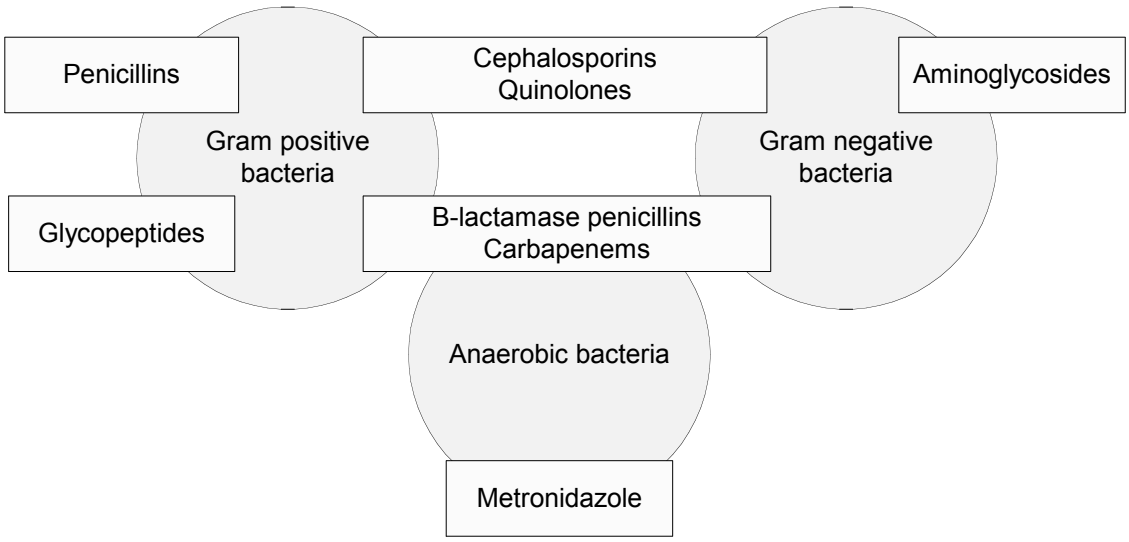

Figure 2: Schematic representation of the identification of redundant antibiotics. If carbapenems and metronidazole were ordered concurrently, the metronidazole would be considered unnecessary and redundant as the carbapenem will cover anaerobic bacteria.

Identification of redundant antibiotics can take place at the level of class of pathogen (e.g. gram positive) or at the level of species (e.g. gram positive S*taphylococcus sp.*), when C&S results are known.

2.4.7. Pharmaco-dynamic modelling

Pharmaco-dynamic and pharmacokinetic modelling software can be used to predict a patient's response to antibiotics and estimate the dose needed to produce the desired response, with minimum toxicity. This can be integrated with the pathology information system where drug blood levels for certain antibiotics are recorded, as well as patient information such as age, weight, sex, infection source, immune status (Shojania *et al.* 1998; Vincent *et al.* 2009).

2.4.8. Reducing IV antibiotic use through an early switch to the oral route

Promoting the IV to oral route switch to reduce the consumption of IV antibiotics allows earlier removal of IV catheters or lines, which are independent risk factors for infection (MacDougall & Polk 2005). Line removal also permits an earlier discharge from hospital. CPOE facilitates automatic discontinuation of drugs after a set period, or it may offer a reminder to a clinician to renew a prescription after a set period has elapsed. CPOE also facilitates conversion to the oral route in two ways: either a daily report allows identification of all patients on IV antibiotics and their prescription start dates, so that patients can then be discussed with each clinician; alternatively, it may allow automatic conversion to the oral route, provided certain conditions are fulfilled, unless otherwise directed by the clinician. This would require integration with a hospital electronic health record.

2.4.9. *Clinician education and feedback on prescribing patterns* (MacDougall & Polk 2005)

General education of clinicians about the appropriate use of antibiotics and the effects of misuse in terms of resistance, opportunistic infection rates and increased costs may improve the treatment of infection through increased awareness. Individualised feedback can be provided in relation to prescribers' rate of compliance with guidelines. Targeting feedback on prescribing patterns and their compliance rates may also help improve the standard of prescribing, particularly when linked with outcome measures such as length

of stay (LOS), morbidity or mortality. Collection of the data to identify prescribers who need detailing is easiest with electronic surveillance or CPOE.

2.4.10. Antibiotic or Antimicrobial Stewardship

As outlined in this section (2.4), CDS interventions can take many different forms. Together they form the basis of *Antibiotic Stewardship.* This has been described as an "ongoing effort by a health care institution to optimise antimicrobial use among hospitalised patients in order to improve patient outcomes, ensure cost-effective therapy and avoid adverse sequelae of antimicrobial use (including antimicrobial resistance)" (MacDougall & Polk 2005). Antimicrobial stewardship links diagnostics, drugs, resistance, benchmarking, education and infection control (Fishman 2006). (See Figure 3.) Key to the concept of antimicrobial stewardship is the multi-disciplinary team: clinical microbiologists, microbiology pharmacists, clinical pharmacists, infection control nurses, hospital epidemiologists, microbiology laboratory staff, ICT personnel with a speciality in microbiology ICT systems and hospital administrators (Cook *et al*. 2004; MacKenzie *et al*. 2007; Rybak 2007). No single strategy is sufficient: a multi-pronged, multi-disciplinary approach is required.

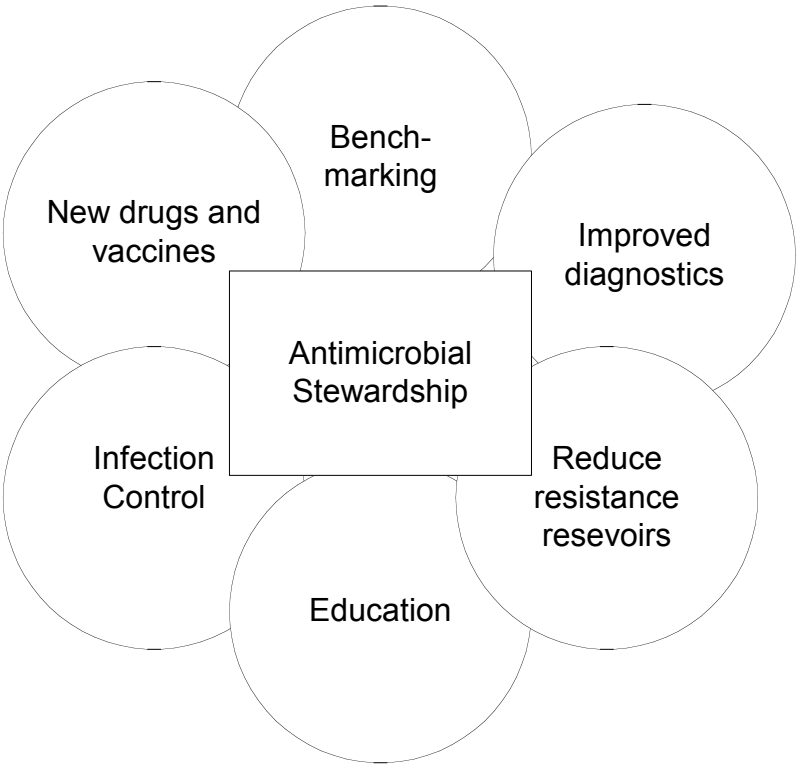

Figure 3: Antibiotic stewardship and reduction of antimicrobial resistance. Adapted from Fishman (2005).

With the recent focus on infection and resistance by many agencies, there have been many recent publications on antibiotic stewardship. Antibiotic stewardship guidelines have been recently published by the Infectious Disease Society of America and the Society for Epidemiology of America, which together promote the use of computerised CDS to reduce inappropriate antibiotic use (Dellit *et al*. 2007). Draft stewardship guidelines are in development for Ireland and the HSE has increased the number of infectious diseases healthcare professionals employed in hospitals through the Strategy for Antimicrobial Resistance in Ireland (SARI) initiative.

In conclusion, there are many different ways in which CDS can be, and has been, applied in the domain of infection. All of these interventions can be classified broadly under the term Antimicrobial Stewardship. Many of these interventions can be performed electronically through CDS provided directly in CPOE or using other means such as audit of transactions in the pharmacy ICT system.

2.5. Measuring antimicrobial drug use

It is very difficult to measure the appropriateness of antimicrobial drug use and even more difficult to meaningfully compare practice between different populations and organisations, which exhibit different levels of case complexity and differing microbial prevalence and resistance rates. To overcome this, the Defined Daily Dose (DDD) was developed (WHO 2009). This is the amount of a drug used to treat one standard patient for one day, for the principle clinical indication (reason for use) for that drug. It is often expressed per 1,000 or 100 patient days or bed-days in the in-patient hospital population, to allow direct comparisons of drug consumption between populations. The WHO has adopted the DDD as their standard system for measuring and comparing antimicrobial drug consumption. DDD tables are published by the WHO. (See appendix II.) The overall DDD for a population or organisation is calculated by combining measurements for each individual antimicrobial drug.

Antimicrobial stewardship programmes usually assume that too many doses, and, by extension, DDDs, of antibiotics are used. The objective is therefore to minimise this figure, while standardising it across similar organisations and populations. It is important to recognise that the DDD result does not indicate how appropriate a hospitals antibiotic prescribing is, only how much they have consumed. The area in which DDDs have found

application is in estimating the relative effectiveness of interventions, by calculation of the relative reduction in the DDD, in matched study patient cohorts.

In this study, it is intended to

- calculate the DDD rates for a specific patient population,
- estimate the ideal DDD for these patients based on the antibiotics guidelines,
- calculate the difference, in order to project the reduction in antibiotic use, if the hospital guidelines had been used to guide treatment in all patients.

2.6. Making computerised CDS successful

At the most basic level, designers of CDS must be able to assess which processes would benefit from automation associated with decision support (Sintchenko & Coiera 2003). Automating an inappropriate task will reduce the likelihood of its usefulness and therefore its acceptance. Tasks which rely on complex information and which are characterised by relatively independent information pathways are more likely to be suitable for automation and therefore exhibit success. As discussed in section 2.4, many of the interventions to improve the diagnosis of infective pathogens and the associated use of antibiotics are amenable to automation. However, computerised CDS requires significant resource inputs, and failure of a system can result in substantial financial losses, loss of time, and loss of reputation. It is crucial, when designing, implementing and using a computerised CDSS, that features critical to success are taken into consideration and evaluated on an ongoing basis (Bates *et al*. 2003).

Any form of CDS, whether manual or automatic should be easy to access, fit into existing workflows, be easily understood, be clinically meaningful, produce recommendations which are easily implemented, provide added benefit in terms of patient care and at an institutional level, be integrated with hospital information systems, be easy to maintain and easy to manage (Bates *et al.* 2003). Clinicians will not use CDS that does not fit into an existing workflow. CDS that is not transparent will not convince clinicians of the benefit of the recommendations. CDS needs to be evidence-based, and directly applicable to real patients (Sittig *et al.* 2008), hence the exploration of Bayesian networks based on real and local data, to diagnose and treat infection. Clinicians will use and trust CDS that improves their knowledge base (Ash *et al.* 2003), and changes in behaviour will be made

possible, especially, if this behaviour results in a perceived improvement in patient care, reduction in workload or more efficient working processes.

CDS needs to exploit patient information that is already recorded in information systems (Sittig *et al.* 2008). The Hospital Information System (HIS) needs to use common codes to facilitate the linkages between the patient administration system (PAS), the pharmacy information system, the radiology information system (RIS) and the laboratory information system (LIS). Examples of common codes would include:

- PAS – medical record number (MRN), date of birth.
- LIS – pathogen codes, antibiotics codes for sensitivity data, code for source of biological sample.
- Pharmacy – codes for drugs in the form of the virtual therapeutic moiety (VTM - the standard chemical name of the antibiotic), unique identifier for each antibiotic product, prescription field codes for dosage form, size of dosage unit (e.g. milligram), number of units per dose, dose frequency, treatment duration / total number doses
- RIS – codes for physiological body areas, which may represent an infection focus.

Using common codes will allow the construction of database elements and linkages for the application of CDS.

Heath Level 7 (HL7) is emerging as the electronic transmission standard for healthcare information in Ireland, between the primary and secondary sectors. (Healthlink / HSE 2009). Any CDS applied would need to be HL7 compatible.

Summary of Chapter 2

Pathogens such as bacteria can cause infection in patients and this may be associated with increased morbidity and mortality: infections may need to be treated using antibiotics. The likely infective organisms need to be identified and empirical therapy initiated, followed by de-escalation of antibiotics when laboratory cultures are made available. Inappropriate antibiotic use is associated with increased costs and increased antimicrobial resistance. There are many different forms of CDS aimed at improving antibiotic use. Antimicrobial stewardship has emerged as a multi-disciplinary strategy to promote good antibiotic practice. Most CDS interventions are amenable to automation. Changes in the

overall DDD figure for an institution can be used to express the effect of antimicrobial stewardship interventions. When implementing a computerised CDS, it is important to consider critical success factors during the project design, planning, implementation, and maintenance stages. Consideration should be given to emerging standards to future-proof the CDS and facilitate inter-operability.

3. Chapter 3: Literature review

Overview of Chapter 3

This chapter will critically appraise the literature detailing interventions to improve the identification of infective organisms and the appropriate treatment of infection, comparing projects where possible. It will go on to discuss the different CDS models used in the domain of infection, their application and their limitations, concentrating on the two most advanced projects, TREAT and HELP. This will be followed by a discussion of the media through which CDS is provided.

3.1. Interventions to improve the predictive diagnosis of infection and antibiotic prescribing

This section will describe the research reported in the literature about the effect of CDS on identification of the probable pathogen and on choice of antibiotics.

3.1.1. Meta-analyses

It has been recognised that no single type of intervention is sufficient in improving the prediction of pathogens and empirical antibiotic use. Antibiotic stewardship covers all types of intervention and recent publications have examined the absolute and relative effectiveness of these.

In a meta-analysis of controlled trials of antibiotic interventions, several strategies were found to correlate with improved use of antibiotics, such as academic detailing (individualised physician education), physician feedback, compulsory approval, including electronic approval, and the use of guidelines. Direct comparison is made difficult due to variability in trial design (Parrino 2005). A 2005 Cochrane analysis found mixed results for most types of interventions. However, the focus of the analysis was not the hospital and it did not examine the use of hospital antibiotic guidelines (Arnold & Straus 2005). A 2009 Cochrane analysis also found equivocal results for the effects of interventions (Davey *et al.* 2009).

3.1.2. Comparative studies

The University Hospital of Pennsylvania has published controlled data on how multi-disciplinary team interventions improve clinical outcomes, reduce antibiotic and hospital costs and improve patient outcome (Fishman 2006). Their interventions included dissemination of guidelines, restriction of certain drugs, prescription surveillance, pharmaco-dynamic modelling, streamlining and education.

Buising *et al* (2008) compared paper guidelines to academic detailing and a web-based CDS algorithm for pneumonia and found that in the early stages, the computerised CDS was better than academic detailing at improving antibiotic prescribing (Buising *et al.* 2008a). However, a study in John Hopkins found that intensive individualised detailing resulted in an increase in appropriate prescriptions from 43% to 74% in a before and after study, and a decrease in inappropriate but effective orders from 30.4% to 6% (Kisuule *et al.* 2008). One limitation is that this study did not examine if the effect was long-term. To be effective, it is acknowledged that detailing must be done continuously, due to the fast turnover of non-consultant hospital doctors (NCHDs), who are responsible for most drug orders.

Sinchenko *et al* (2004, 2005) have conducted several studies in the area of CDS. Their research shows that CDS with microbiology data provided the best agreement with expert advice in the area of Ventilator-Associated Pneumonia (VAP), when compared to no support, guidelines alone or laboratory results alone. Prior to this the same group also researched provision of CDS using a handheld device in the ICU in a 6 month before and after study and found that it decreased LOS and reduced the total consumption of antibiotics.

3.1.3. Use of guidelines

Guidelines have been used in medicine for many years. As the reason for infection and its treatment are complex, guidelines found application in this clinical domain from an early stage. Guidelines suggest a likely range of pathogens for an infection source and recommend appropriate antibiotics to which pathogens are likely to be sensitive. Guidelines have been produced nationally (e.g. Australia, UK), by expert consensus based on clinical evidence, and locally, at a regional and institutional level. In most

teaching hospitals, paper guidelines are issued and maintained by the microbiology department. However, guidelines alone are insufficient to ensure that treatment is appropriate, as clinicians may not adhere to them, for example, using personal preference and experience to guide their choice of drug. As with any software tool, making them meaningful and easy to use and access increases the likelihood of their uptake by clinicians and other healthcare professionals. In the UK, NHS Nottingham has been active in providing comprehensive microbiology guidelines through their intranet and via the internet (Nottingham City and University Hospitals Microbiology Departments 2009). One meta-analysis has shown that provision of antibiotic guidelines is associated with a lower rate of antimicrobial resistance (Zillich *et al*. 2006).

Further developing guidelines into algorithms and decision trees can increase the specificity of microbiology guidelines. Clinical data can be used to construct decision trees, which are then used in the diagnosis of infection. A particularly problematic area is bacteraemia in neutropenic sepsis, which occurs in highly immunosuppressed patients, such as those with leukaemia or undergoing chemotherapy. Ammann *et al* (2004) described and validated such a system. However, as with any model, it is only as good as its training data, so choice of variables is important, as is using as large a number of data points as possible to generate valid results.

3.1.4. IV to oral therapy switch

A small study encouraged physicians to use oral rather than IV quinolone antibiotics when prescribing, if certain clinical and dietary conditions were fulfilled. The CDS was provided via the web at the point of physician order. It resulted in an increase of oral therapy and a reduction in IV therapy (Hulgan *et al*. 2004). The TheraDoc® integrated software also facilitates the IV to oral switch through the use of alerts embedded in the CPOE (TheraDoc® 2009).

3.1.5. Antibiotic approval systems

Restrictions on the use of certain antibiotics, unless approval has been given by a microbiologist or pharmacist, has had success in reducing the use of targeted antibiotics and total antibiotic cost. This may consist of verbal approval through telephone, computerised approval, such as requiring a specific indication to be given before the antibiotic is dispensed, allowing initial treatment by requiring approval within a certain

number of hours, or recommending changes in therapy based on laboratory results (Cook *et al.*2004; White, Jr. et al. 1997). An American study generated a daily report on all patients receiving more than one antibiotic through their pharmacy system and these were reviewed by a microbiology pharmacist who then approved the drugs as appropriate (Glowacki *et al.* 2003). Bringham and Women's hospital require physicians to choose an indication for restricted antibiotics. They observed a reduction in the frequency and duration of vancomycin use (Shojania *et al.* 1998).

The Royal Melbourne Hospital has published data on electronic antibiotic approval. Buising *et al* (2008b) found that their iAPPROVE program resulted in a fall in the use of restricted antibiotics, a reduction in MRSA and resistant *Pseudomonas* species. They also demonstrated a reduction in cephalosporin use and improved adherence to national guidelines (Richards *et al*. 2003). Another approval system, IDEA^3(S), also in Melbourne,has replaced 48% of all telephone consultations. It uses an evidence-based rules system for specified clinical indications to approve or refuse antibiotics (Grayson *et al*. 2004). A survey of clinicians' perceptions of the system showed that they found it easy to use, it integrates well into their workflow and improves guideline adherence. However, the response rate was only 58% and this may exhibit an inherent bias for the system in favour of those who find it useful. In addition, there was positive correlation between higher satisfaction scores and the rate of use of the system by clinicians (Zaidi *et al.* 2008).

The effect of approval systems goes beyond simply restricting supply, unless certain clinical criteria are fulfilled by the patient. Systems may be subject to gaming or override. There is a valuable element of physician education and academic detailing, which contributes to future improved prescribing by that physician (MacDougall & Polk 2005). Moreover, many studies have demonstrated that restricting certain antibiotics reduces total antibiotics costs, and this is thought to have a knock-on effect on the overall rate of resistance. In contrast, a recent meta-analysis of studies in the USA found that restrictive formularies were associated with an increase in the overall rate of antimicrobial resistance (Zillich *et al.* 2006). More specifically, restriction of a single agent may result in over-use of an alternative in its stead; resistance to this antibiotic may rise, while resistance to the original falls. This has been observed in practice (Allegranzi *et al*. 2002b). The phenomenon has given rise to the theory of antibiotic cycling, where alternatives are used for fixed periods then switched (Allegranzi *et al.* 2002a).

3.1.6. Surveillance

Mc Gregor *et al* (2006) investigated the use of inappropriate or insufficient antibiotics using existing prescriptions and microbiology laboratory data to indicate which patients required intervention, in the form of an alert. This was a non-randomised, blinded, controlled study, which found that expert intervention reduced costs. Interestingly, instead of focussing on the prescriber, the decision support was aimed at the microbiology team who then contacted the medical team to change antibiotics as recommended.

An American study of patients, who received more than one antibiotic concurrently, found that 71% of patients of patients were receiving at least one redundant (unnecessary) antibiotic. The pharmacy was able to identify this through automatic computerised surveillance (Glowacki *et al.* 2003).

Patients can also be surveyed for infection risk through integration to the LIS and the PAS. Patients with a prior history of MRSA can be identified on admission then screened, segregated and treated appropriately. Integration with the PAS also allows identification of a patient's origin, in particular if they have come from a nursing home or other hospital, so that appropriate antibiotics can be tailored to the most likely pathogens (Shang *et al.* 2000).

3.1.7. Pharmacokinetic CDS

There are several key antibiotics that require careful dosing based on weight or body surface area, kidney function, liver function and blood levels: this is necessary to achieve a good therapeutic effect while avoiding toxicity. The study of this is called pharmacokinetics. Kidney and liver function are important because these drugs are highly dependent on these mechanisms for excretion from the body. Dose calculators may be incorporated into CPOE for these drugs e.g. gentamicin (Chan *et al.* 2006). A Cochrane review of computerised dose adjustment CDS found benefit accruing to pharmacokinetic CDS. Several of the studies in the meta-analysis investigated dosing of antibiotics (Durieux *et al.* 2008). However, CPOE has also been associated with inadvertent errors: to avoid this, CDS needs to take the latest measurements of all recent relevant biological

parameters into consideration when making a dosing recommendation (Eslami *et al*. 2006).

Summary of 3.1

There are many different examples of interventions to improve the identification and appropriate treatment of infection. These include the provision of local, tailored antimicrobial guidelines, physician education, physician feedback, surveillance of antimicrobial prescriptions in an organisation, antibiotics approval systems and restrictions, promotion of the IV to oral route switch and the use of pharmacokinetics to individualise the dose of antibiotics. Individual studies and meta-analyses have shown mixed results. However, large difference in trial design make direct comparison between trials difficult.

3.2. Models of CDS used

This section presents a range of CDS models used in the area of infection, starting with the simplest form (rules-based) and progressing to the most complex, and / or mixed models. Many different models have been used either singly or in combination, in the provision of antibiotic CDS. The two most successful systems, TREAT and HELP, are multi-modal; they are discussed in-depth.

3.2.1. Rules-based and related systems

Rules–based systems use Boolean characteristics to build a hierarchical decision tree. The original antibiotic decision support system, MYCIN, was developed in the 1970's but never used in clinical practice (Shortliffe *et al*. 1975).

Fuzzy logic (FL) is a form of rules-based analysis that has been used to identify cause and effect in healthcare, in combination with traditional statistical methods. FL uses an extension of Boolean rules where *Yes / No* becomes *More / Less / Maybe*, allowing uncertainty or degrees of concordance with a rule to be expressed. Inter-relationships between variables can be established and fuzzy sets can then be derived using *If / Then* rules. FL has been used to establish bacterial pathogens and propose treatment.

A simple score system to differentiate between two different forms of meningitis (an infection which carries a high mortality rate, was designed. It used 3 clinical laboratory values to predict the need for antibiotics. A reduction from 58% to 22% was projected in inappropriate antibiotic use in viral meningitis (De Cauwer *et al*. 2007).

Another study investigated 5 clinical decision rules to distinguish aseptic (non-infective) from bacterial meningitis to avoid inappropriate antibiotic use (Dubos *et al.* 2006).A simple rule-based score was investigated, to see if it could reduce the rate of prescriptions for sore throat. The authors found a drop of 21% in prescriptions using this simple intervention, compared to control (McIsaac & Goel 1998).

Nosocomial infections are a major cause of mortality in hospitals. Joch *et al* (2001) describe a rules-based warning system to identify such infections early using parameters already available in the HIS. Challenges included interfacing the microbiology laboratory system with the HIS using HL7 and defining standard vocabulary through the use of a dictionary.

FL uses overlapping and contradictory rules to represent "grey areas" not fully covered by Boolean logic. One system using fuzzy rules for identifying Gram negative infection using demographic details has been described (Cundell *et al*. 2001).

The Italian MERCURIO system is rules-based. It mines the laboratory database to develop the knowledge base (EMSIS): this is used to identify the likely pathogen, and then antibiograms are validated in order to recommend antibiotics (Lamma *et al*. 2006). It is useful in quickly identifying nosocomial or other unusual patterns of infection.

The in-house computerised CDS system of the Regenstrief Institute in the USA is rules-based (Friedlin *et al.* 2007). The designers have identified the fundamental building blocks for their rules (i.e. rules which are independent of other rules) and their role in construction of the rules-base. Their system is fully integrated with CPOE, their LIS and HIS. It provides guidance, alerts, alarms, time-dependent reminders and prompts for information if required so that rules can be applied to patient information.

The ADVISE system in Melbourne has been developed over a number of years (Thursky *et al.* 2006). This is a user-centric system, which is integrated into the LIS. It provides

advice on empirical treatment, prints out culture results for ward rounds and recommends de-escalation treatment when pathogens are isolated. The CDS was built using a rules base with rules for various types of clinical isolate e.g. sputum. It also uses real biochemistry measurements of renal dysfunction to suggest dose reductions. In an ICU study, over a 6 month period, there was a reduction in total antibiotic use and also in the use of newer broad-spectrum antibiotics, improved streamlining of treatment when results became available and fewer antibiotic-pathogen mismatches (Thursky *et al.* 2006). The CDS element of ADVISE is an extension of their antibiotic approval system, iAPPROVE (Buising *et al.* 2008b).

A dual system was used to determine macrolide (a class of antibiotic) sensitivity in paediatric patients with CAP. This was prompted by rising rates of macrolide resistance among cases of *Strep. pneumoniae*. Two models, one based on logistic regression analysis and a second based on a "fast and frugal" decision tree were evaluated, and both showed high specificity in determining which patients would not require treatment with a macrolide antibiotic (Fischer *et al*. 2002).

3.2.2. Artificial Neural Networks (ANNs)

ANNs are constructed by classifying data into primary characteristics and further sub-classifying them into subordinate characteristics, using historical patient data. ANNs can capture complex and non-linear inter-relationships between parameters.

Cooper *et al* (2005) directly compared many different models in the domain of CAP, and found, when the full set of training data from all variables was used to inform the database, that the model with the greatest Receiver Operator Curve (ROC) area was a neural network model. However, the authors comment that it should be further tested against different models. Neural networks have been applied in the area of wound infection, where clinical criteria were used to predict wound infection (Lammers *et al.* 2003). The UK HIV network has used 30,000 cases in developing an ANN for Human Immunodeficiency Virus (HIV) resistance and prediction of sensitivity depending on viral genotype (Larder *et al.* 2008). Neural networks have been compared and found superior to logistic regression for the prediction of MRSA (Shang *et al.* 2000).

3.2.3. Case-Based Reasoning (CBR)

CBR has been extensively used in medicine, and medical intuition is largely based on thought processes similar to CBR. When applied to a model for CDS, it uses a cycle of Interpretation / Retrieve / Reuse (known as the IRR cycle), so that existing experience informs current decision-making (Bichindaritz 2006). CBR systems can be made more robust and kept up to date by inputting parameter values from new and locally relevant clinical cases. It has been used in the areas of diagnostic imaging, intensive care, oncology and medical diagnoses.

The ICONS project was based on CBR where the case database was searched for a matching patient and suggestions about antibiotics made based on this. It was validated in the ICU setting. The reasoning behind CBR is that "similar problems have similar solutions". Gierl and his team note that a flow of sensitivity results from the laboratory into the knowledge base is necessary to keep antibiograms and antibiotic recommendations up to date and locally relevant (Gierl *et al.* 2003; Heindl *et al*. 1997) (Schmidt & Gierl 2001). Their antibiotics recommendations also incorporate a rules-base.

The West Virginia University Hospital has developed a "bug-drug logic table" to map pathogens to antibiotics (Mullett & Thomas 2003). By using a large amount of historical laboratory data, they have been able to develop a large case knowledge base, which is continually updated with more recent results. Patients are matched to similar cases in the knowledge base by the use of parameters such as surgery type, clinical area, demographics and focus of infection. Surrogate antibiotics and class sensitivities are used to expand the knowledge base through extrapolation of results from those antibiotics that are directly tested. The system can be used to predict empirical therapy for infections before the pathogen has been identified; in a 6 month clinical validation trial, it chose appropriate antibiotics in 86% of cases compared to 66% for physicians (Mullett *et al.* 2004).

3.2.4. Causal Probability Networks

Causal Probability Networks (CPNs) are based on Bayesian inference and have been used frequently in healthcare, principally as a diagnostic aid. Bayesian inference uses Bayes' theorem to assign marginal and posterior probability to an event based on observed

variables. This data is used to construct a domain probability chart, which links characteristics with the probability of their indicating a specific effect. CPNs may be constructed of large numbers of variables and are suited to complex domains. They are very useful where data relationships are non-linear and clinical criteria are influenced by more that one clinical parameter simultaneously.

CPNs have the ability to generate results based on a database that can be updated with further information, as it becomes available. This may be done manually or through direct retrieval from other informatics systems, such as the LIS. The more data that is used, provided it is appropriate to the hypothesis, the higher the probability that the suggested outcome is correct. CPNs can also be tailored to make recommendations based on the probable problem diagnosed. A disadvantage of CPNs is that they use large amounts of processor space, which can result in long reaction times. This makes it difficult to integrate the support seamlessly into a clinical workflow. A distributed environment located within and without a hospital has been proposed to overcome this (Androulidakis *et al.* 2006).

Work on CPNs dates from the 1990s but has progressed significantly in recent years. The model has been most successfully applied in practice in the multi-modal TREAT and HELP systems.

(a) TREAT

Andreassen *et al* (1999) describe a CPN model for urinary tract infections in which laboratory data was used to construct the model, suggest the likely pathogen, recommend treatment and calculate utility based on prognosis. They also describe how CPNs from different biological sites can be combined through overlap. CPN is a useful approach as it can meaningfully combine qualitative and quantitative data within the knowledge base. This characteristic also influenced Lucas *et al* (2000), who designed a probabilistic network associated with a decision theoretic approach in the diagnosis and treatment of VAP in the ICU setting. They describe elsewhere how this multi-modal system, is suited to application in the domain of infection, especially where there is missing knowledge (Schurink *et al.* 2007; Visscher *et al*. 2008). Steinmann *et al* (2008) also developed a surveillance system for VAP, which they validated, although the logic behind the program is unclear from their publication.

The TREAT system (Zalounina *et al.* 2007) is an international programme based on CPNs and follows on from earlier work published by Andreasson and his team. It uses maps of local bacterial prevalence and their sensitivities to predict pathogens and recommend antibiotics to which they are likely to be sensitive. It also uses information on resistance patterns to predict likely cross-resistance between antibiotics for a given pathogen, allowing an informed recommendation to be made should the treatment of first choice fail. Where data is missing, probable values can be assigned by the system by using standard distribution based on existing data. It can differentiate between local relationships and general relationships. TREAT is unique in that it recommends treatment based on clinical prognosis and cost, including avoided future costs such as those associated with longer admission times and future resistance. As a result the users can directly assign costs saved to TREAT at an individual patient level. TREAT also establishes likely resistance through cross-resistance prediction using the knowledge base.

Initially TREAT was assessed using a cohort study, followed by a randomised control trial. It performs reasonably well in the prediction of pathogens, when they are subsequently identified by positive culture (Paul *et al*. 2006, 2007). One early study with TREAT was conducted in urinary tract infections: TREAT prescriptions were appropriate in 88.5% compared to 60.8% for physicians (Kristensen *et al*. 1999). It has been assessed in an environment with intermediate and high rates of resistance where the level of appropriate prescribing was 70% for TREAT compared to 57% for physicians (Paul *et al.* 2006). Costs fell due to the use of cheaper, narrower-spectrum antibiotics. It has also been assessed in an area of low pathogen resistance (Kofoed *et al*. 2009). In this latter study, the rate of appropriate prescriptions was 86% for the CDS against 66% for unsupported physician prescriptions. However, the total amount of antibiotics used in this study actually rose while costs were similar. In this study, TREAT recommended antibiotics for patients for whom physicians did not. TREAT can also be used to predict bacteriaemia and to classify it as low, moderate or high risk, the classification of which has implications for diagnosis, treatment and outcome (Paul *et al.* 2006). TREAT has so far been validated in three different populations with different pathogen distributions; the authors have commented that the CPN model allows a high level of local configuration of the knowledge base, both qualitatively and quantitatively, resulting in a high level of accuracy.

(b) Health Evaluation through Logical Processing (HELP)

The Latter Day Saints (LDS) hospital in Utah has been one of the pioneering institutions in developing and implementing computerised decision support. They have been developing their HELP (**H**ealth **E**valuation though **L**ogical **P**rocessing) system since the 1970s, although it origins date back to the 1960s (Pryor *et al*. 1983). It is fully integrated into the HIS and is thus able to use variables from the PAS, the CPOE system and the LIS in its application of CDS. Thus, the antibiotic consultant uses data from microbiology cultures, biochemistry, haematology, radiology, pharmacy and the patient's electronic patient record (EPR) (Bissell 1999). The microbiology module is based on CPNs combined with decision rules (based on laboratory data) and some case matching, (also based on laboratory data). The rules are updated monthly by a team of experts. Laboratory data from the last 5 years are used, then deleted from the database. Initial searches are made using data from the previous 6 months; if this does not provide a good match or if there are insufficient cases, historic data from the 5-year database are used. When cases are matched, the probability of infection by different pathogens is analysed using twenty parameters and six variables (Evans *et al*. 1993). Where data are missing, the system can use average data from past matched cases (Evans *et al.* 1998, 1999). LDS have applied the HELP system to guide not only the empirical therapy of infection and subsequent de-escalation, but also antimicrobial prophylaxis for surgical procedures, through integration into their HIS (Burke 2001).

There are three levels of logic:

(a) Pathogen probability for each combination of variables and likely antibiotic susceptibility.

(b) Rules guiding appropriate choice of antibiotic
- if one agent will cover > 80%, this is recommended up to a maximum of 5 different antibiotics
- if coverage for any one agent < 80%, two or more are suggested.

(c) Treatment specific information such as
- Allergies
- Availability of oral access to give antibiotics by the oral route if possible
- Renal function to assess dosage requirements
- Costs.

Physicians can also view guidelines, antibiograms and antibiotic monographs.

One of the group's earliest publications discussed Therapeutic Antibiotic Monitor (TAM) alerts (Pestotnik *et al.* 1990). Following culture results, pharmacists would notify clinicians of the results and make recommendations within three categories: prescribed antibiotic / pathogen mismatch, no antibiotics required or pathogen resistance to prescribed antibiotics. This project showed limited success in this study with only 38% of clinicians changing treatment to that advised within 24 hours. It did highlight nonetheless, that in half the cases, the physician was unaware of the laboratory results for their patient.

An early randomised controlled trial (RCT) by Evans (1994) showed a 17% increase in pathogen sensitivity to antibiotic treatment. They also showed an appropriate compliance rate of 94% for the CDS against 77% for the clinicians. Physicians were surveyed and acceptance of the software was good. A larger 1996 study used 7 years data from all patients admitted to LDS. It demonstrated reduced use of antibiotics per patient, reduced acquisition costs, fewer adverse drug events, reduced mortality, better pre-operative prophylaxis timing, reduced number of excess doses in surgical patients (Pestotnik *et al.* 1996).Two years later they published data from the ICU, a clinically complex area with respect to infection and its treatment. This showed reductions in drug allergy alerts (by 76%), the incidence of over-dosage (by 17%), antibiotic sensitivity mismatches (by 94%), the number of antibiotic-associated adverse events (by 85%) and reductions in antibiotics costs, total costs and length of hospital stay (Evans *et al* , 1998, 1999). In a specific trauma ICU study, despite low uptake of CDS (46% of antibiotic prescribing episodes only), they demonstrated improved antibiotic use, reduced adverse effects and reduced antibiotics costs (Evans *et al.* 1998). A 1999 publication showed that making antibiograms available to physicians through the antibiotic consultant programme promoted changes in prescribing practices (Burke & Pestotnik 1999).

LDS has published methodologies for the diagnosis of pneumonia and deciding whether or not to admit the patient, one based on natural language modelling using radiology reports, and another based on a Bayesian network for diagnosis and management. They found that combining these two approaches in a multi-modal model gave the best results (Aronsky *et al*. 2001; Aronsky & Dean 2001). A key point is that the quality of the data used to guide decision-making must be of a sufficient standard to be applied to the model. LDS have also adapted the same logic to the prescribing of antibiotics in paediatric

patients, where they found an improvement in accurate dosing, a hugely complex area. In addition, a large reduction of 59% in pharmacists' interventions was recorded, and antibiotic costs fell by 9% (Mullett *et al*. 2001). They have extended antibiotic prescribing directly into the theatre to improve the choice and timing of pre-operative prophylactic antibiotics through CDS embedded in the CPOE system (Burke 2001). This resulted in a timing compliance rate of 99% by 1999, compared to 72% in 1998.

The HELP system has been made available commercially.

A related group in the same city has developed the *TheraDoc® Antibiotic Assistant®* in association with the University of Utah for commercial purposes (Reynolds 2003; Warner, Jr. *et al.* 1999). This is available through the internet (their LE version which is evidence-based) or can be integrated into a HIS to provide real time recommendations to clinicians, based on microbiology C&S results, and oral switch alerts (*TheraDoc®* website.) The software company claims that participating hospitals have avoided infection-related deaths and reduced antibiotics costs significantly. A community-based group investigated the uptake of this CDS by rural hospitals. On average, uptake was variable, as the findings were skewed by poor uptake of the CDS by all but one hospital, which did show a large improvement in the quality of prescribing (Stevenson *et al*. 2005). In general, however, research publications about *TheraDoc®* are lacking.

Summary of 3.2

Different models have been used in the provision of computerised CDS in the domain of infection. Modelling a dynamic clinical condition is complex and multi-modal models have been used to address the deficiencies of individual models. Rules-based systems. ANNs, CBR, and CPN have all been used in various settings. The most comprehensive applications that have been validated on a large scale are the HELP system in Utah and the TREAT system in Europe, largely based on CPNs but also featuring case-based and rules elements. Both have been developed and validated over many years to a stage where they are now used to provide computerised CDS at all stages in the management of infection. Future CDS in integrated systems will most likely follow this path as CPN-based systems have been shown to be robust and have been validated across the spectrum of bacterial infection.

3.3. Medium through which CDS is provided

CDS can be provided in several different ways: by direct intervention, by using paper forms or treatment algorithms, through CPOE (restrictions, alerts and alarms) or by the use of stand-alone software. CDS can be provided via the hospital intranet, perhaps using wireless systems, or through the world-wide web (www). Different types of media are suited to different interventions. Some examples are given below.

3.3.1. Personal Digital Assistants (PDAs)

John Hopkins hospital trialled a handheld web-based antibiotics guideline (ePocrates ID) and found that antibiotic prescribing improved in the handheld group. The trial cohort consisted of house doctors, and the study illustrated how making the support available at the point of care is critical to its acceptance and use (Bochicchio *et al.* 2006).

Samore *et al* (2005) investigated CDS in the community, comparing public education with individual physician education and CDS provided to primary care physicians for respiratory tract infections. They found a reduction in the use of antibiotics in the CDS group. The CDS consisted of paper guidelines and PDA-based software (*TheraDoc*®). In a later study by the same group, Rubin *et al* (2006) found that the rate of adherence to guidelines was high for the PDA-based CDS in isolation. However, unlike the earlier study, there were no baseline data for comparison purposes, although they did demonstrate that more intense users of the PDA-based CDS had higher rates of adherence to guidelines.

3.3.2. Paper

A study in Utah used a simple paper form to provide CDS for the admission decision in CAP and found that the rate of hospitalisation dropped from 13.6% to 6.4%. The CDS was used in 90% of 463 cases during the study period in four health centres. A further comparative study showed a comparative reduction in 30-day mortality in centres where the CDS was used at 11% compared to 14.2% (Dean *et al.* 2000, 2001).

South *et al* (2003) described how printing common antibiotic treatment guidelines on a small card which could be clipped to an identity badge, improved the treatment of cellulitis (a skin / soft tissue infection) and pneumonia, two of the most common hospital

infections, while reducing the cost of 3rd generation cephalosporins, a class of antibiotics, by 50%.

3.3.3. Web-based systems

A large knowledge base was used to develop a rules-based system for *Toxoplasmodium* in Austria, and made available though the internet. This allows physicians to diagnose the disease and identify the recommended treatment (Kopecky *et al.* 2007). The ADVISE antibiotic approval program discussed is also web-based, as is the Nottingham system (Buising *et al.* 2008a) (Zaidi *et al.* 2008) (Nottingham City and University Hospitals Microbiology Departments 2009).

3.3.4. Pharmacy information system

An American study investigated the application of rules into their CPOE system, when a particular expensive anti-fungal drug was prescribed. These rules were used to generate a prescriber alert. It did not however, prohibit prescribing of that item. While the CDS did reduce the rate of prescribing of this particular agent, it was not as effective as direct pharmacist intervention (Collins 2004). Glowacki *et al* also used the pharmacy system to monitor for redundant antibiotics (Glowacki *et al.* 2003).

Summary of 3.3

Different media have been used to provide CDS. Historically, systems have been paper-based or verbal. CDS has also been provided electronically, but in a non-interactive form. More recently CDS has been provided electronically at the point of prescribing in CPOE. This is ideal, as it proactively directs the prescriber towards an actionable recommendation, using all available information relevant to the drug order. The mechanism through which the CDS is provided depends on many factors but the importance of being able to practically provide and maintain an intervention within resource restrictions should not be overlooked.

3.4. Standards and inter-operability

The application of standards is important in all form of computerised CDS. Standards provide a benchmark; they facilitate communication, data analysis and inter-operability. One of the most difficult aspects of inter-operability is the development of a drug

database that can be used for prescribing as well as for logistic processes such as dispensing and drug distribution. The former process involves an abstract drug and dosage regimen, the latter a physical product whose manipulation must be facilitated by the CDS or other medicines management system.

Another area of research is that of medical terminology: coding medical terms in order to link them to measurable parameters in a consistent and clinically meaningful manner. Systematized Nomenclature of Human Medicine **(**SNOMED) and Natural Language Processing are two approaches to standardisation. SNOMED has been adopted by the UK's National Health Service (NHS) as their preferred medical coding system. In Ireland, hospital admissions are reported using the International Classification of Diseases, 10th Revision, Clinical Modification, known as ICD-10-CM. Chapter 1 of this deals with infection.

A continuous problem in the application of CDS is linking the clinical presentation and management of a patient with a valid drug database. The French have developed a drug database called VIDAL which uses Anatomical Therapeutic Classification (ATC) codes for use in their web-based PRESGUID project. This facilitates access to clinical practice guidelines and associated treatments (Dufour *et al.* 2004). The NHS has recently launched their Dictionary of Medicines and Devices (dm+d) which lists all medicines and devices available in the UK, using unique identifiers; this is SNOMED compatible (BNF.org 2009). Their use of a standard VTM to describe drugs allows the dm+d to be used as a database for CDS and CPOE. The *TheraDoc*® Antibiotic Assistant is also SNOMED compatible (TheraDoc® 2009). HL7 may prove to be useful in facilitating inter-operability between healthcare organisations (Jenders *et al.* 2008).

It is important that any computerised CDS be developed with interoperability and integration with other information systems as a priority, so that it provides added benefit, fits into the electronic healthcare record and facilitates surveillance, research and clinical audit.

3.5. Limitation of the literature

Publications on CDS in the domain of infection are difficult to compare, due to differences in intervention design and outcome measurements. The most important clinical end-point, patient outcome, expressed in terms of LOS, mortality or morbidity, is rarely addressed. Yet improving patient outcome is the primary objective of any form of CDS in any domain.

In a 2009 Cochrane meta-analysis of antimicrobial stewardship, there were inconclusive results regarding the effect (immediate or sustained) of different types of interventions. The authors commented on poor study design and difficulties in comparing studies due to large differences in parameters and outcome measurements (Davey *et al.* 2009).

In a 2007 review, Shebl *et al* examined publications that directly evaluated the CDS literature. A major finding was that there were very few RCTs of computerised CDS, due to the difficulty of conducting them in this environment. Before and after studies were more common but even these were few. Studies were difficult to compare as end points differed. Although they concluded that computerised CDS showed good potential for benefit, this was not always borne out in the literature and differences in study design made meta-analysis unfeasible. Designing an RCT in this domain would be unethical, which may explain their dearth in the medical literature (Thursky 2006). The same author comments on the lack of patient-centeredness in study outcomes.

In an earlier meta-analysis, MacDougall *et al* (2005) critically examined the literature on antibiotic interventions, finding that, even with a single intervention type, outcomes were variable. The authors found a poor rate of compliance with Cochrane standards of study design, with a high percentage of papers describing simple before and after studies. As prescribing is a dynamic process, a series of time points are required to robustly establish an effect is due to an intervention. Multiple interventions types, and their overlapping effects, exacerbate difficulties in study design.

Andreasson (1999) notes that the quality of a CPN, and therefore its relevance to clinical practice depends on how well it predicts actual events. Calculated probabilities should be compared with those observed to ensure validity. Validity may be illustrated by the use a

ROC, which estimates the rate of false negatives and false positives for a model, given many different scenarios.

In a review of papers reporting a reduction in medication errors due to stand-alone CDS, Kaushal et al (2003) found that there were significant effects for the two studies reported by Evans and colleagues in LDS; these studies were unusual in having significant results, and the authors commented that most other studies were not powered sufficiently to demonstrate significance.

3.6. Critical success factors and barriers to successful uptake of computerised CDS

Critical success factors need to be met in order to optimise the human-machine interaction in computerised CDS. These may be related to technology, design, human characteristics or organisational culture. While the machine element is predictable and controllable, the human element is highly variable and not necessarily open to influence. The design of the CDS plays an important role in user reaction and uptake.

Key to the success of CDS is the appropriate assessment of work processes for automation. Certain processes, in particular when complex or when there are several discreet information pathways, lend themselves well to automation as the final task complexity is reduced for the operator (Sintchenko & Coiera 2003). The nature of the task and degree of complexity will also influence what type of CDS is most appropriate. An ICU study found that more complex tasks used a more computational form of CDS and less complex decisions were made using simpler electronic clinical guidelines (Sintchenko & Coiera 2006).

Bates *et al* (2003) published the "ten commandments" for "effective clinical support" in 2003, outlining how CDS exhibiting these features could improve the practice of evidence-based medicine. These ten characteristics were extracted from implemented CDS systems in the literature and have been adapted from Bates (2003) for the purpose of this study.

1. Speed is crucial
    - Slow computer systems mitigate their usefulness: this is important with respect to data retrieval and information processing

2. Address needs, including latent needs
    - Identify what is required, both the obvious and the implied
3. Fit into the user's workflow
    - CDS which interferes with work processes will not be used: it should integrate seamlessly with workflow and if possible, confer additional benefit on the work process
4. Make it user-friendly
    - The user must be able to understand and use it easily; avoid user fatigue through reducing unsolicited alerts or integrating them into the workflow
5. Recognise that physicians exhibit inertia
    - Once a prescription has been initiated, it is difficult to stop, and this inertia increases as the time spent on the task gets longer: if a process must be stopped, do it at an early stage
    - Make tasks actionable, making task completion by the user more likely.
6. Offer alternatives – changing a user's direction is easier than stopping them
    - See (5); suggest alternative course of action; useful in directing choice of drug during CPOE
7. Keep it simple
    - Strike a balance between simplicity and clinical meaningfulness
8. Only ask for additional information if absolutely necessary
    - Interrupts workflow; use information already stored elsewhere where possible (EHR, LIS, RIS, PAS, Pharmacy information system, automated text processing)
9. Monitor impact, request feedback, respond
    - Ask the users what they think and need, act on this
10. Manage and maintain the knowledge base
    - It is crucial that CDS recommendations are correct, up-to-date and appropriate: this can be achieved through good and robust database management.

In another meta-analysis, some more critical success features were identified (Thursky 2006):

11. Justify the decision support provided (evidence, reasoning)
12. Provide incentives to use such as complex calculations, correspondence

13. Ensure local user involvement in design and development of CDS
14. Accompany computerised CDS by normal education.

Kawamoto *et al* (2003, 2005) undertook a meta-analysis of published CDS trials in order to identify which features independently correlated with improved clinical practice. The authors found these to be:

- Automatic provision of CDS at the point of care
- CDS which gave actual recommendations (if it relates to an actionable task)
- CDS provided through the use of ICT
- CDS integrated into clinical workflow.

Ash *et al* (2003) published a consensus guideline on success factors for CPOE, broadly dividing their criteria into different categories: motivation, vision and leadership, costs, workflow integration, value to users, staging and project management, technology, training and support, evaluation and improvement.

Sittig *et al* (2008) identified 10 challenges to the implementation of effective CDS. Key to these is the way in which CDS is made available to the user (user interface, alerts, recommendations), how it integrates into workflow (seamless interventions, automated text processing) and how uses pre-existing information about the patient where possible (automated text processing, information already held on hospital ICT systems or in the electronic health record). The authors note that there is a huge potential to mine existing data both within and between organisations, to generate the knowledge base for CDS. They also comment on the existence of data silos, where knowledge and architecture is available only locally, as a major barrier to the dissemination and uptake of CDS. Microbiology is particularly ripe for data mining due to the great number of microbiology culture results, even at an institutional level.

Ebert (2007) has examined barriers specific to the domain of infection. These include a fear of under-treating the patient, uncertainty about the source of the infection (often the first symptoms are non-specific), lack of documentation of the suspected or proven indication and patient pressure. An antibiotic may be prescribed “just in case”. Some of this can be overcome by physician education about probable pathogens and bacterial antibiotic susceptibility patterns. Patients may improve on an antibiotic, even if it is not the drug of choice, and clinicians may be unwilling to change. Crucially, however,

physicians must have confidence in the recommendations of the CDS. Younger, less experienced doctors are more likely to rely on CDS for recommendations, compared to older prescribers, who act intuitively based on past case experience. A Dutch study found that disagreement with guidelines and peer pressures were further barriers to adherence to antibiotic guidelines (Schouten *et al.* 2007).

A 2005 review specifically examined the application of the Human Factors discipline in CPOE design and implementation (Saathoff 2005). Their main recommendation was that users should be consulted and involved from the outset. Clinician trust must be established, work processes must be made more efficient, for example through the use of popular order sets for users and graphic interfaces must be relevant, based on natural language and intuitive. Task analysis is key to understanding processes. Training and user support is also critical to system success. It is also important to establish credible leaders who are also clinicians or other healthcare professionals. The project team should have inter-complementary information and communication technology (ICT), clinical and administrative skills.

One of the first CPOE systems in the USA was at the Regenstrief Institute. A recent publication on design of their in-house CDS system lists speed, work process integration, feedback and the ability of the user to override an alert as key to success (Friedlin *et al. 2*007). Graham *et al* (2008) assessed intranet-based clinical practice guidelines (CPGs) for CAP and neutropenic fever in the Emergency Department setting for usability and "sensibility" for physicians. Although they established that physician found the neutropenic fever CPG more useful, no conclusions were drawn about why certain physicians were unlikely to use the CPGs at all. Stevenson *et al* (2005) found that in a community hospital CDS project, organisational difficulties were responsible for poor uptake of the intervention.

Zaidi *et al* (2008) surveyed users about their perceptions of an antibiotic approval system. They found that users who perceived that the system was easy to use (access, integration into workflow), reliable and relevant to practice, were more likely to us it. During the design phase of this CDS element of this system, ADVISE, a user-centred approach was taken, involving potential end-users opinions and suggestions (Thursky & Mahemoff 2007).

Summary of 3.6

In summary, the literature has shown that there are many characteristics common to successful computerised CDS. These need to be identified and evaluated in the context of the organisation. When subsequently designing and developing the computerised CDS, it is vital to take these critical success factors into consideration as far as is practical. If these success criteria are not fulfilled or only partly fulfilled, it may negatively impact on the successful uptake of the CDS by its intended users, primarily prescribers.

Summary of Chapter 3

There are many different types of electronic and manual interventions to improve the diagnosis of infection and antibiotic prescribing described in the literature. These are of varying effectiveness. Together, they may be described as antimicrobial stewardship. Several different models have been used in the design of antibiotics CDS: rules-based systems, FL, decision trees, CPGs, CBR, ANNs and CPNs. Newer systems often incorporate more than one model type. Well-designed and meaningful trials are uncommon and studies are therefore difficult to compare. The two main systems, HELP and TREAT, are primarily based on CPNs but also use elements of other model types. Interoperability and standards for computerised CDS have not been addressed in the literature. Different media have been used in antibiotic CDS. In order for computerised CDS to be successful, there are several conditions that should be fulfilled, in the context of the model used and the organisational environment and culture.

4. Chapter 4: Methodology

Overview of Chapter 4

Chapter 4 discusses the conduction of the literature search. It then details the data collected and its rationale in terms of the study objectives. It explains how the compliance rate with the antimicrobial guidelines was measured; the calculation of antibiotic consumption expressed as DDDs; and its associated cost. It explains how the rate of antimicrobial consumption, and the cost thereof, is calculated for guideline compliant antibiotic use. It then explains how these figures are extrapolated to give projected results for a 12 month period. Finally, it goes on to discuss the choice, design and assessment of the CDS intervention for implementation.

4.1. Literature search

The medical literature (PubMed, Cochrane) from 1999 to 2009 was searched using combinations of the following key words and acronyms, using MeSH terms: decision, support, CDS, CDSS, prescribing, prescription, electronic prescribing, electronic prescription, physician order entry, CPOE, order entry, antibiotic, antimicrobial drug; medications, antimicrobial stewardship, antibiotic stewardship, diagnosis, empirical treatment, infection, sepsis, restricted antibiotics, antibiotic formulary.

The reference lists of relevant publications were also trawled to find further applicable publications, including some from before 1999, where they were of major importance to this study.

If two or more papers by the same author(s) discussed the same subject, the more relevant and / or scientific was chosen. If two or more papers described exactly the same study, only one was included.

4.2. Study population

A fixed number sample of patients presenting to the author's hospital Emergency Department with lower respiratory tract infections (LRTIs) was investigated (n=14) over a 6 week period. This group of patients was chosen due to the relatively high rate of presentation of this type of infection and the previously reported low rate of compliance

with antimicrobial guidelines by prescribers in the author's hospital, which led to a high rate of inappropriate antimicrobial use.

4.2.1. Objective

The objective was to

(a) Identify those antimicrobial drugs prescribed for each patient's LRTI.
(b) Establish if this complied fully with hospital guidelines with respect to choice of antibiotic(s), the dose(s) thereof, the route and the duration of treatment with IV, and subsequently oral medication. Patients were considered to be either compliant or non-compliant: partial compliance was not measured.
(c) Measure the number of units of each antimicrobial drug used to treat the infection.
(d) Calculate the total amount of antimicrobial drugs used (1).
(e) Identify the appropriate treatment for each individual patient in accordance with hospital guidelines.
(f) Calculate the total amount of antimicrobial drugs which would have been administered had the correct drugs been used to treat the infection (2).
(g) Calculate the difference between (1) and (2).
(h) Establish the total number of LRTIs admitted during the previous 12 months. Extrapolate the results to give a figure for 1 year.

4.2.2. Data collected

The following information was collected for each patient in the study:

(a) Identifier – patient's initials plus MRN.
(b) Allergy to any antimicrobial drugs.
(c) Diagnosis (in these cases LRTI).
(d) History of chronic obstructive pulmonary disease (COPD).
(e) Source of the admission (community, hospital, or nursing home).
(f) Details of each antimicrobial drug prescribed, their dose, form, route of administration and number of doses administered.
(g) Whether or not a microbiology consultation took place.
(h) Cost of one dose of each antimicrobial drug used.

A sample of the data collection form is given in Appendix I.

4.2.3. Data analysis

From this information, it was possible to establish for each patient:

(a) Which drugs were prescribed for each patient.
(b) Which guideline-compliant antimicrobial drugs should have been used.
(c) If the initial treatment was in accordance with antimicrobial guidelines.
(d) How many doses of each drug were given; how many were given intravenously and how many orally.
(e) How many DDD units of each antimicrobial drug were administered for each route.
(f) How many DDD units of each recommended antimicrobial drug would have been used had the guidelines been followed and assuming the switch to oral therapy was made at 48 hours as per normal practice: most patients treated appropriately have sufficiently improved at 48 hours after initiation of treatment, to allow a switch to oral treatment, from IV.
(g) The difference between these two measurements of total DDD.

A cost analysis of the use of actual antibiotic used was performed and the same cost for guideline-compliant antibiotics was calculated for comparison purposes.

Based on these figures, it was possible to take total admission figure for all pneumonia and COPD patients from the Hospital Inpatient Enquiry (HIPE) system and extrapolate them for all admissions over the 12 months of 2008.

The calculation of the DDD for each drug is based on a WHO-published table. The DDDs for all study drugs are listed in Appendix II.

4.2.4. Exclusions

(a) Any patients who have received a consultation from a microbiologist – their recommendations may deviate from the guidelines as such patients generally are more complex and may have multi-organ infections.
(b) Patients with multiple infections requiring treatment with the same antibiotics as would be used for an LRTI, as this may necessitate stepping outside the guidelines to avoid the use of antibiotics with overlapping spectra of activity.

(c) Cystic fibrosis patients: empirical treatment is based on a mixture of complex treatment algorithms and microbiology consultations which take the patient's medical history into consideration.

4.3. Development of an electronic antimicrobial drugs guideline for the empirical treatment of infection

4.3.1. CDS models proposed

Given local considerations and limitations on time, resources and expertise, the two options for development of an electronic interactive form of the guidelines were to:

- design a wizard which would solicit the required demographic and clinical information and make a recommendation based on this information
  OR
- design a series of web pages with links at each major decision, to guide prescribers to the correct treatment option for their patient.

Their advantages and disadvantages are presented in Chapter 5 (Results).

4.3.2. Testing of prototype CDS

Validity, with respect to recommendations for the successful implementation of a computerised CDS system, was assessed. (See Chapter 3.6.) These success criteria comprised:

1. Speed
2. Address needs, including latent needs
3. Fit into the user's workflow
4. Make it user-friendly
5. Recognise that physicians exhibit inertia, make tasks actionable
6. Offer alternatives
7. Simplicity
8. Only ask for additional information if absolutely necessary
9. Monitor impact, request feedback, respond
10. Manage and maintain the knowledge base
11. Justify the decision support provided (evidence, reasoning)
12. Provide incentives to use such as complex calculations, correspondence

13. Ensure local user involvement in design and development of CDS
14. Accompany computerised CDS by normal education.

An additional three characteristics were added by the author as being desirable:

15. Ease of access to the intervention
16. Ability to facilitate clinical audit
17. Integration with other existing ICT systems.

Summary of Chapter 4

Chapter 4 has outlined the methods used to research the study topic in the medical literature. It has discussed the design of a small study to estimate local compliance rates with antimicrobial guidelines in the domain of LRTIs, the rate of antibiotic consumption in the form of DDDs and its associated costs. It explained the calculation of these same figures for guideline-compliant antibiotic use. It went on to outline the choice of CDS intervention type available to the author, and the rationale for the choice of the intervention, in addition to plans for assessing it for compliance with critical success features as outlined in Chapters 3.6 and 4.3.2.

The results from Chapter 4 will be given in Chapter 5 and further discussed in Chapter 6.

5. Chapter 5: Results

Overview of Chapter 5

Chapter 5 presents the results of the study. These include the rate of compliance with the antimicrobial guidelines in LRTIs, the level of consumption of antibiotics and their associated costs. It then compares these to the corresponding guideline-compliant estimates and calculates the difference in terms of antibiotic consumption and cost. It projects antibiotic consumption for the specified indications over 12 months and extrapolates the number of DDDs that would be used, and their associated costs, over a 12 -month period. It then discusses the rationale for the choice of CDS intervention chosen along with its design. The intervention is also assessed against critical success factors drawn from the literature.

5.1. Calculation of compliance rate, DDDs and their associated costs

5.1.1. Study population

Patients presenting to the hospital Emergency Department with an LRTI requiring admission, over 6 week period, were investigated. Four were excluded: 2 had other co-infections treated with antibiotics also used to treat LRTIS and 2 were the subject of a consultation with microbiology. The remaining patients, n = 14, had some form of pneumonia (n = 12) or an exacerbation of COPD (n= 2). Two patients received concurrent treatment for urinary tract infections. They were not excluded as different antibiotics were used to treat this second possible infection, as there was no potential for treatment crossover.

The study patients age profile was as follows:

- Age less than 60 years n = 2
- Age between 60 and 80 n = 6
- Age greater than 80 n = 6

This profile would be typical of patients admitted to hospital with an LRTI.

5.1.2. Compliance with hospital antimicrobial guidelines

Of the 12 pneumonia patients it was assumed that all were severe as their severity was not documented and they were started on IV antibiotics. This was taken as the standard guideline treatment.

Three patients had hospital-acquired pneumonia (HAP) and 9 had CAP.

The overall rate of compliance with the hospital empirical treatment guidelines for COPD or pneumonia was 21%. (See Chapter 4.2.1 for details on how compliance was assessed). Neither of the COPD patients was prescribed guideline-compliant drugs on admission. Of the HAP patients, 1 was compliant with guidelines and of the CAP patients, 2 were compliant. This represents a rate of 0%, 33% and 22% for COPD, HAP and CAP respectively. It is worthwhile noting that the Emergency Department doctors saw most patients initially, and they were then admitted under the team on-call. The admitting team is usually one of the Medical teams, but not usually the Respiratory Medicine team. The latter would be expected to show a greater knowledge of the appropriate treatment of LRTIs.

5.1.3. DDDs of actual antimicrobial drug use compared to those for guideline antimicrobial drug use

Table 1 shows the total DDD for each drug actually used and compares it to the total DDD for guideline-compliant antimicrobial drug use. It shows that actual antimicrobial drug use was 45.21 DDDs lower (17.09%) than projected guideline-compliant antimicrobial drug use. This may be explained by the under-treatment of patients: in 2 cases, only one of the two recommended antibiotics for pneumonia was prescribed and in 2 other cases, the patients were switched to oral treatment after less than 24 hours of IV antibiotics, (at least 48 hours IV treatment is usually indicated before switching to the oral route entirely). For both the oral and IV routes, it was found that a lower number of doses were actually used for each route (134 oral doses and 231 IV doses respectively) than would have been used if the guidelines had been fully followed (144 oral doses and 290 IV doses).

In order to calculate the guideline-compliant equivalent total DDDs, it was necessary to assume a treatment course of 10 days (which is the usual duration) or, in the event that the

actual course was less than 10 days, the actual duration was used. It was also assumed that the IV treatment would be switched to the oral route after 48 hours as switching earlier is not appropriate in severe pneumonia, but most patients improve significantly at between 24 and 48 hours.

Eleven patients were used to calculate DDD usage. Three patients out of the original 14 were excluded from the analysis as:

- one developed further complications requiring antibiotics
- it was not possible to establish the number of doses of an antibiotic given to a second patient
- for one patient with pneumonia, it was not possible to identify if it was CAP or HAP, for the purposes of guideline-compliant DDD calculation.

Name of drug	*Route*	*DDDs actually used to treat the patients*	*Projected DDDs compliant with guidelines*	*Variance*
Amoxicillin	Oral	0	15	15
Amoxicillin	IV	0	6	6
Cefuroxime	IV	0.5	0	(0.5)
Clarithromycin	Oral	61.5	119	57.5
Clarithromycin	IV	1	0	(1)
Co-amoxiclav	Oral	101	85.5	(15.5)
Co-amoxiclav	IV	22	27	5
Levofloxacin	Oral	9	0	(9)
Piperacillin / tazobactam	IV	24.29	12	(12.29)
Total		**219.29**	**264.50**	**45.21**

Table 1: DDDs for each drug actually used and the projected DDDs for antimicrobial drug use, had the guidelines been followed.

In summary, not enough antibiotic doses were administered to patients. This is accounted for by two events: only one of the two recommended drugs was used in 2 cases; patients were switched to oral therapy after less than 48 hours in 2 other cases.

5.1.4. The cost of the drugs administered to study patients compared to the costs of guideline-compliant antibiotics

Table 2 shows the cost of all doses of each drug actually used and compares it to the cost of all doses for antimicrobial drug used, had the guidelines been fully followed and had the patients been switched to oral treatment after 48 hours. Older antibiotics such as co-amoxiclav and oral antibiotics such as clarithromyin tablets are less expensive than newer drugs or antibiotics, especially when given IV. Table 2 shows that the actual antimicrobial drug use cost was 47% higher than the cost of the antimicrobial drugs which would have been used, had the guidelines been followed.

Name of drug	*Route*	*Total cost (€) of antibiotics used*	*Total cost of guideline-compliant treatment (€)*	*Variance (€)*
Amoxicillin	Oral	0	2.70	2.70
Amoxicillin	IV	0	9.36	9.36
Cefuroxime	IV	5.52	0	(5.52)
Clarithromycin	Oral	65.19	126.14	60.95
Clarithromycin	IV	22.98	0	(22.98)
Co-amoxiclav	Oral	86.96	73.53	(13.33)
Co-amoxiclav	IV	122.10	149.85	27.27
Levofloxacin	Oral	28.53	0	(28.53)
Piperacillin / tazobactam	IV	722.63	357	(365.63)
Total		**€1,053.91**	**€718.58**	**€(335.22)**

Table 2: Cost of all antibiotics actually used compared to the cost of guideline-compliant antimicrobial drug use.

The increased cost of the antibiotics actually used in the study patients can be almost fully explained by the inappropriate use of the broad-spectrum antibiotic piperacillin / tazobactam. It has a role in the treatment of HAP, but not in CAP or COPD. In this study, it was prescribed inappropriately for 2 patients at a daily cost of €25.50.

5.1.5. Hospital admissions over a 12 month period

The total number of HIPE admissions for acute pneumonia in the previous 12 months was 42. Table 3 shows the estimated difference in total DDDs and their cost for this group of

patients, allowing an estimate of the effect on guideline compliance in this group of patients over a 12-month period.

No. of patients	*Difference in DDDs for study patients compared to guideline-compliant DDDs*	*Difference in costs for study patients compared to guideline-compliant costs*
11	45.21	€(335.22)
42	172.62	€(1279.93)

Table 3: Values for the difference in DDDs and their associated costs, extrapolated to give estimates for a 12-month period.

5.1.6. Conclusion

The study showed that not enough doses of antibiotics, expressed as DDDs, were used to treat LRTIs in study patients. Conversely, the inappropriate use of the expensive drug piperacillin / tazobactam, rather than guideline-compliant cheaper antibiotics, resulted in increased costs. Following the guidelines would have resulted in more DDDs being used, but at a lower cost per patient, as less expensive antibiotics would have been used.

5.2. Development of an electronic antimicrobial drugs guideline for the empirical treatment of infection

5.2.1. Choice between the two proposed forms of CDS

The two forms of CDS practically available were an antimicrobial wizard and intranet-provided antimicrobial guidelines in HTML. The advantages and disadvantages of each of the proposed computerised decision support systems are listed below. This influenced the final choice of CDS.

(a) Antimicrobial Wizard

This is a programme that would ask the user for specified information, then recommend a treatment. See Chapter 4.3.1.

Advantages:

+ Data entry is on one page only
+ Fast to use
+ It provides an exact recommendation for that patient

+ There is no decision-making processes required on the part of the prescriber
+ There is a potential to link to PAS so patient's demographic details appear automatically
+ It can be provided through hospital intranet or internet
+ There is a potential to record queries using a log provided the prescriber uses a personal log-in and enters each patient's details
+ There is a potential for microbiology to be notified when the system records certain diagnoses or when certain antimicrobial drugs are recommended
+ There is a potential for microbiology to link queries with C&S samples sent for analysis
+ There is a potential to provide reduced dose recommendations, to take account of kidney failure, through a link to the LIS
+ There is a potential to add in an allergy function, so that prescribers are alerted when drugs to which the patient has an allergy are ordered.

Disadvantages

- It is moderately complex to design – programming is required
- There is a need to design the graphical user interface using web-design
- There is a need to programme the rules-base
- The recommendations are not actionable, although this could be a future development
- If using a log, there is a need to set up a database with defined fields for recording information
- If recording queries, there is a need to see up some kind of look-up or reporting function
- There is a need for an interface if taking data from the LIS or patient details from the PAS
- There is a need to provide some kind of look-up for information purposes only, without entering patient information
- There is little potential for user education
- It is possibly expensive to implement

(b) <u>HTML pages on the hospital intranet</u>

Advantages:

+ It is simple to use, navigate and understand
+ It is fast to use

+ It is very flexible
+ It is easy to host on hospital intranet
+ It is easy to design
+ There is no programming required
+ It is easy to maintain as no ICT support required
+ It provides good prescriber education and support of natural prescribing thought processes
+ There is a potential to attach a counter for the number of hits, to see how often the CDS is being consulted
+ No interfaces are required
+ There are no additional costs or resources required

Disadvantages:

- There may be multiple pages for users to get to final recommendation, although good design should be able to limit this to 3 pages
- The recommendations are not actionable
- There is a reliance on the user to interpret information correctly
- It is not possible to know how often it is being used for real patients
- There is no log of queries available – audit is not possible
- As it is not linked to a patient, microbiology intervention or links with C&S samples is not possible
- There is no potential for individualised patient alerts, such as allergies
- Interfaces with the PAS or LIS are not relevant.

Outcome

It was decided to proceed with designing the guidelines in a HTML format as this was the only option that was within the scope of the project, given resource constraints (time, expertise, financial, structural). Another crucial advantage of HTML over a wizard was the author's opinion that a wizard which answers only one question without passing through a series of intermediate questions and which does not facilitate access to related, but not directly relevant, information, would be a poor clinical teaching tool. As the author's hospital is a university teaching hospital, this was felt to be a major drawback in this setting.

5.2.2. Design of the HTML pages

Using the exiting guidelines, a series of pages in HTML were designed for COPD and CAP. All are illustrated in Appendix C. This can be represented as:

(a) Home page

On the home page there are:

- one clink links to all diagnoses
- one click links to all other topics
- one click link to a full index.

The home page is a standard template with design features that are constant to all pages, namely:

- institutional crests
- contact numbers for the microbiology and infection control teams
- standard medicines information resource links
    - British National Formulary
    - St Vincent's Healthcare Group Medicines Guide
    - Irish Compendium of Medicinal Product Information for Healthcare Professionals
- left panel for quick links to any topic at any time.

(b) Respiratory tract infection page

There is a one-click link to each respiratory diagnosis page, in this case:

- exacerbation of COPD
- CAP
- hospital or nursing home acquired pneumonia
- aspiration pneumonia
- *pneumocystis iiroveci* (previously *p.carinii*) pneumonia
- etc.

(c) Individual diagnosis page

Each diagnosis page subsequently contains a decision tree for the correct treatment of each patient according to defined criteria. It also contains links for:

- standard medicines information resources for each medication, giving details on preparation and administration, drug interactions, contraindications and precautions for use
- guidance on the switch to oral microbial drugs
- guidance on dose reduction in kidney failure or liver failure for each drug.

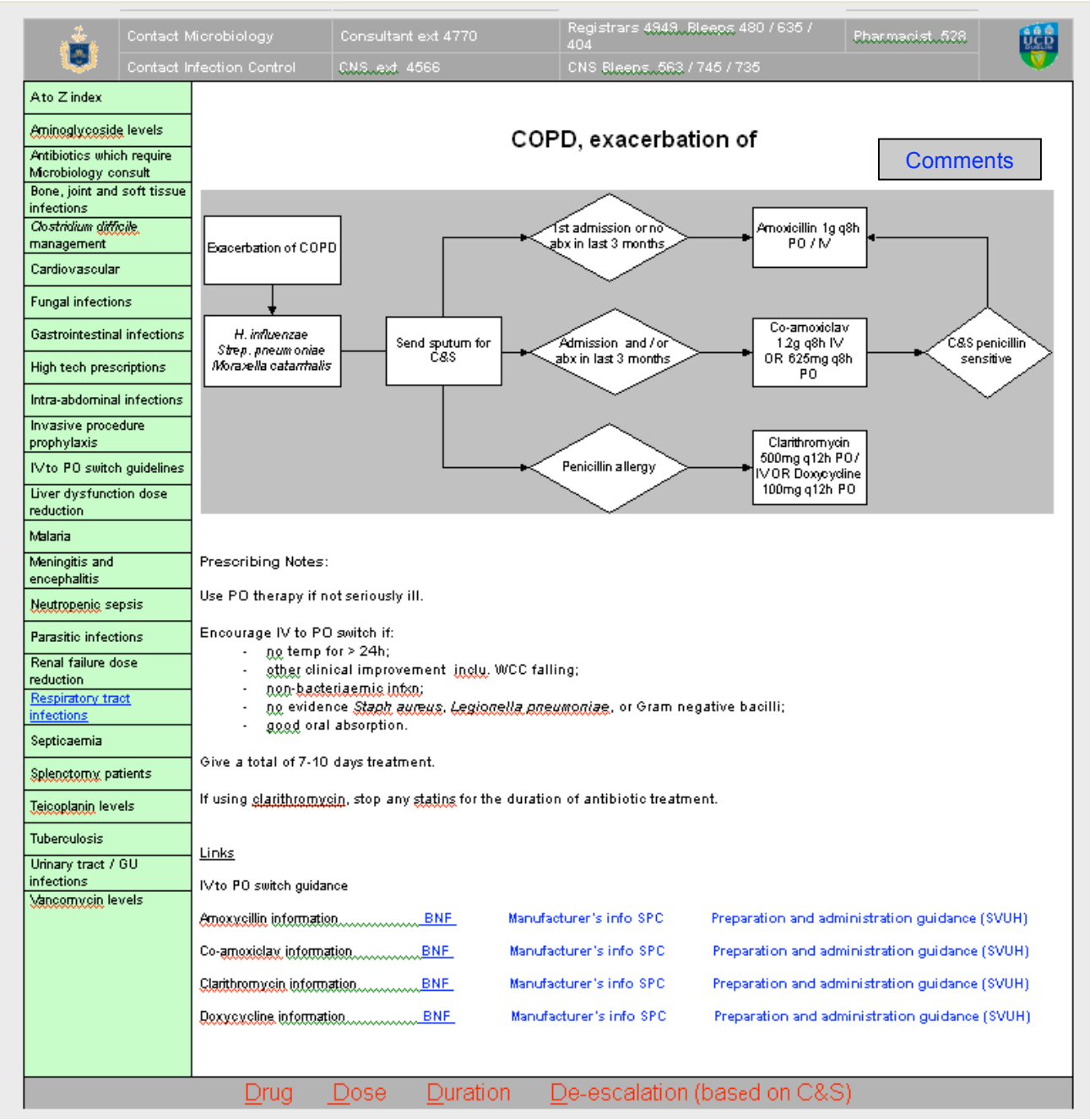

Figure 4: HTML page for exacerbation of COPD.

5.2.3. Testing of prototype CDS

(a) Assessment of critical success factors

Compliance with recommendations 1-14 for the successful implementation of computerised CDS systems was assessed with respect to the HTML pages and the antimicrobial wizard. (See Chapter 3.6.) An additional 3 desirable features were added by the author: A(i) to A(iii) in Table 4 below. All criteria / features were graded from 1 (worst) to 5 (best). The results for the HTML pages are shown in Table 4 and those for the wizard in Table 5. They are however, subjective, being the opinion of the author. The CDS scores 43 out of a possible 70.

Success criterion	*Score*	*Comment*
1. Speed	4	Will depend on speed of hospital intranet, which is usually reliable. The small byte size of each page means they are fast to load. The design of the menu panel to the left and the fact that it is present on each page means that the user is only ever one or two clicks away from a final recommendation.
2. Address needs, including latent needs	4	The model provides the user with knowledge of all parameters used in arriving at a recommendation.
3. Fit into workflow; end point is actual recommendation	1	Not present at bedside at point of prescribing or when diagnosis is actually made. Not actionable. In all cases prescribers are shown the drugs they should prescribe or if the recommendation is unclear, a request that they consult a microbiologist (contact details provided).
4. Ease of use and navigation	5	Very straightforward to use. Clean design and a lack of clutter. Clinically meaningful terminology used. The design of the menu panel to the left and the fact that it is present on each page means that the user is only ever one or two clicks away from a final recommendation.
5. Avoid inertia	0	This CDS is passive. Recommendations are not actionable.
6. Offer alternatives	0	This CDS is passive.
7. Keep it simple – fit it on one screen	5	The complete recommendation fits on one screen.

Success criterion	*Score*	*Comment*
8. Ask for information only if absolutely necessary	Not applicable	The model does not ask for any information
9. Feedback and its incorporation into design and content	3	Feedback e-mail link available.
10. Management of maintenance of the application and of the knowledge base	4	Simple HTML pages can be maintained by anyone with word-processing and file management skills. No ICT support is required. Some coordination with the information technology department is required with respect to file management and hosting.
11. Evidence-base is clear to the user, clinically relevant	3	While each recommendation is not fully referenced to the medical literature, the home page explains the rationale for the guidelines and its applicability to the local setting and local patterns of microbial prevalence and susceptibility.
12. Offer incentives to the user	2	Complex guidelines e.g. for meningitis, will be provided in full and in a print-friendly format. Renal, body surface area and liver dysfunction calculators are provided.
13. Local user involvement in development	3	Developed locally but user opinions will need to be sought at a more advanced stage.
14. Complement usual prescriber education	5	When operational, normal prescriber education will proceed as usual but will incorporate end-user training for the CDS package.
A(i) Ease of access	2	Readily available through hospital intranet as terminals are available in all clinical and office areas. There may be some difficulty with accessing a computer on demand, but this is being addressed. It could also be made available through the internet, if this is thought appropriate. However, it is not integrated into an order communications or CPOE system and therefore prescribers must choose to use it to access it for information.
A(ii) Able to facilitate clinical audit	0	Not possible.
A(iii) Integration with other hospital ICT systems	2	Not possible to interface, but a link may be provided to the LIS.

Table 4: Compliance with recommendations for the successful implementation of a computerised CDS system for the HTML pages.

An additional important advantage of this model is its educational component, particularly for prescribers, but also for other healthcare professionals.

(b) Testing for validity of recommendations

The model was set up fully for CAP pneumonia and exacerbation of COPD. Within these diagnoses, the electronic CDS gave an appropriate recommendation.

All links were fully functional, but not operational.

Summary of Chapter 5

The compliance rate with the antimicrobial guidelines in the study groups was 21%. An insufficient number of DDDs of antibiotics were used: this was attributable to too few individual antibiotics being prescribed and to an inappropriately early switch to oral treatment. Conversely, the cost of the antibiotics used was 47% higher than it should have been, due to the inappropriate use of one particularly expensive drug. If the guidelines had been fully followed, more doses of antibiotics would have been used, but, at a lower overall cost, as less expensive drugs would have been used.

The advantages and disadvantages of an antimicrobial wizard and a series of HTML pages were listed. The prototype CDS intervention chosen and designed was a series of HTML pages for LRTIs. This was assessed against critical success factors from the literature and incorporating three of the author's own desirable characteristics.

Chapter 6 places these results in the context of how to proceed in the near future.

6. Chapter 6: Discussion

Overview of Chapter 6

Chapter 6 discusses the results of the study and how compliance rates with antimicrobial guidelines could be improved in the future.

6.1. Results of the study

6.1.1. Compliance rates

The study has demonstrated that even in a very small number of patients with a common infection with a standard treatment regimen, there is a huge capacity for the inappropriate prescribing of antibiotics. This can have consequences for the patient, ranging from a slower recovery time and LOS to clinical complications from related or other co-morbidities. Inappropriate use of antibiotics, in particular at a sub-therapeutic level, also allows microbes to develop resistance. This can have serious consequences for future patients and the treatment of future infections as the number of available antibiotics to treat a particular resistant microbe is reduced.

In this study, it was found that many patients did not receive the correct combination of antibiotics for long enough. How can compliance rates be improved? As identified by Ebert (2007) and Schouten (2003), there are multiple factors affecting compliance rates with antimicrobial guidelines, from physician preference for certain antibiotics, to fear that using a more narrow spectrum antibiotic might somehow "miss" an infective pathogen. Lack of awareness of the guidelines is also important, as is their immediate availability at the point of prescribing. Pressure of workload and the design of the workflow are related factors. In addition, patients may attempt to influence a prescriber to order an antibiotic or doctors may also may be subject to pressure from their colleagues, feeling obliged to prescribe an antibiotic as indicated by their senior colleague, or because an antibiotic is the one which their other colleagues use routinely to good effect. In addition, doctors are most likely unaware of the current prevalent pathogens in the population or their patterns of antibiotic resistance. Any effort to improve guideline compliance should address all of these factors. It is important for everyone to recognise their limitations and to know where to find information to support them in their care of the patient, in this case, from antimicrobial guidelines or through discussion with microbiology experts.

6.1.2. Setting of the study

As this study focussed on admissions through the Emergency Department, workflow and human factors need to be identified.

a) In the Emergency Department, patients are seen first by a nurse in triage, then by an Emergency Department doctor. The Emergency Department doctors perform a complete patient investigation and document intended treatments, including antibiotics, in the patient assessment documentation.
b) If appropriate, the patient is referred to the medical team on-call who may decide to admit the patient, depending on the severity of the infection and the clinical status of the patient. At this point, a new drug chart is started, with a new antibiotic prescription, separate from the Emergency Department order, which is part of the departmental patient assessment documentation. Antibiotics are often changed at this point and the admitting team may not immediately refer to the existing prescription. This time is critical for the choice of antibiotic treatment and could be a key input time for antibiotic stewardship. In two of the study patients, antibiotics were changed at the immediate time of admission.
c) Emergency doctors see a limited number of different types of infection and tend to be familiar with their treatment. Medical teams, who are based within the hospital proper, see many more types of infection and more complex infections requiring broad-spectrum antibiotics, and may therefore be more likely to use inappropriate antibiotics

6.1.3. Antibiotic consumption

In this study, it was found that the number of DDDs used was less than these which would have been administered, had the guidelines been followed. This was a surprising result, in particular as the guideline treatment period was capped at 10 days, yet of the 11 patients used to extrapolate DDD rates, only 4 were treated for less than 10 days. This increase in guideline-compliant DDDs applied to both the oral use and IV use of antibiotics. It suggests that patients in the study were under-treated. This has consequences for full eradication of the infection (recovery might be slower), possible re-activation of the infection and the development of pathogen resistance. It can also potentially impact on the patient's LOS in the hospital, and the potential to develop other

co-morbidities while an in-patient, such as MRSA or C*lostridium difficile* infection, both of which may result in significant morbidity and mortality. Simply being in hospital reduces patient mobility and this can lead to a risk of deep vein thrombosis or pulmonary embolus. Changed diet, bowel habits and poor sleep patterns also occur in hospital, leading to slower recovery times and increased LOS. Giving a sufficient amount of antibiotic treatment to properly clear an infection is therefore important.

The study found that, although the number of DDDs administered would have been higher had the guidelines been fully followed, the total cost of antibiotics used could have been almost halved (a reduction of 47%), as less expensive antibiotics would be used. Knowing that the overall hospital compliance rate with antibiotic guidelines in the last multi-disciplinary study was in the order of 63% (Sanchez 2009) leads the author to conclude that there may be significant cost-savings to be made from improved guideline compliance in LRTIs, in drug acquisition costs alone, although a more thorough and complete study would be required to quantify this accurately. Such a study has not been done to date. One would also expect knock-on effects on total hospital cost per patient from a reduced LOS and reduced morbidity.

6.1.4. Limitations

This study had many limitations and these must be borne in mind when drawing conclusions. It was extremely limited in scope and design, and was not powered to calculate significant results. Numbers were very small and there was only one clinical indication, LRTI, in patients admitted through one portal, the Emergency Department. The study looked only at the empirical treatment of infection. It was however, within the domain of LRTIs, more complete than the previous existing snapshot study of compliance rates (Sanchez 2009), which measured compliance at a single time point only, rather than over a whole course of antibiotics, as in this study.

In order to estimate guideline-compliant antibiotic consumption rates, it was necessary to make acceptable assumptions about the number of days of IV treatment and the total length of the course of antibiotics. Such assumptions may not reflect reality and are general at best. They assume a standard patient: however, each patient is different and responds to an infective episode and antibiotic treatment differently.

In addition, a clinical pharmacist sees all in-patients regularly: they may identify inappropriate antibiotic use and request the team to change treatment in mid-course. Microbiologists may also advise prescribers based on C&S results from laboratory samples. It would be an interesting study to establish what percentage of patients receiving antibiotics have been subject to a microbiology consultation on request from the patient's medical team, have their antibiotics changed on a pharmacist's recommendations or have biological samples sent for C&S, triggering microbiology advice.

6.2. Future directions in improving compliance

While there is agreement on why doctors do not adhere to antimicrobial guidelines (Ebert 2007), there is less evidence on how compliance can be improved in practice. This is the focus of antimicrobial stewardship and various interventions have been discussed at length in chapters 2 and 3. Interventions in the literature have been applied with variable success. Such programmes vary from the highly complex and integrated HELP and TREAT systems, to simple low technology interventions such as the provision of guidelines in a ready-to-use tool, such as on a small laminated card. Factors critical to the successful implementation of CDS apply equally to interventions in the domain of infection. See Chapter 3.6.

6.2.1. Antibiotic stewardship

In the author's hospital, the antimicrobial stewardship group, due to start work in September 2009, will consider and implement a variety of strategies to improve the use of antibiotics. As outlined in Chapter 2.4, these may include:

(a) providing accessible, easy to use and always up-to-date guidelines on the treatment and prevention of different infection and more generally on the principles of using antibiotics, including through the hospital intranet
(b) increasing awareness though education and feedback
(c) surveying antibiotic use and intervening directly with the team
(d) auditing antibiotic use in targeted audits
(e) focussing on particular teams about their antibiotic prescribing patterns
(f) feeding back C&S results to the team when the pathogen is identified and again when its sensitivity to antibiotics is established

(g) feeding back to prescribers about patterns of infection and the dissemination of antibiograms based on real C&S data to educate prescribers
(h) increasing awareness of the IV to oral switch as a mechanism for earlier discharge and reduced costs
(i) identifying if prescribing patterns are causing nosocomial infections such as *Clostridium difficile* diarrhoea and communicating this to prescribers
(j) discouraging the use of restricted antibiotics and investigating patients using these on a case by case basis.

6.2.2. Choice of CDS intervention

As the author's hospital has neither an integrated HIS or CPOE, the potential for the application of computerised CDS is very limited. As a result, the author chose the HTML-based intervention as one that is easy to implement, exploits existing levels of ICT resources and has the potential to become widely used, if prescribers find it useful and clinically meaningful. The intervention consists of an electronic interactive form of the existing guidelines made available through the hospital intranet.

The intervention has been assessed for compliance with the critical success factors for CDS. (See Chapter 5.2.3.) Its success, however, will depend on user reactions and uptake. At the moment, there are sample pages for "Home" and "Respiratory tract infections" only. As the format will be common to all sections however, prescriber input will be sought at this stage and suggestions to make it better or more clinically meaningful will be assessed and implemented if appropriate and feasible. The agreed template will then be applied to all other infection types. A gap analysis will be performed to identify areas that are not covered and guidelines will be developed for these infections. To date, the format of the HTML pages has been approved by the clinical microbiologists and the hospital management has agreed how and where to host the pages.

It is envisaged that while the author will develop the site, it will be maintained by the specialist antibiotic pharmacist in association with and with the approval of the clinical microbiologist in the hospital. Hospital C&S data will be used to construct and maintain antibiograms in the form of a "bug-drug" table, indicating local pathogen sensitivity or resistance to various antibiotics. This will be made available to users.

Usage of the pages by precsribers will be critical to success. Initially, a counter will be used to calculate the number of "hits". A "comments" button, present on all pages will seek feedback from users. At a future stage, it will be possible to add on a user log-in to identify who is using the site and more importantly, who is not.

This is only one intervention of many although it does represent a substantial project for the microbiology service. It also only targets one factor affecting non-compliance, namely prescriber awareness and education. It will be implemented concurrently with an awareness programme such as posters, oral presentations and quizzes for healthcare professionals. The intervention however, still relies on the user to voluntarily access and use it, during the prescribing process. Other interventions will be required to target other factors affecting poor antibiotic prescribing.

6.2.3. Assessing this intervention

The success of this intervention will be assessed using the results of on-going audits of the clinical use of antibiotics to establish if the introduction of the guidelines has had any impact. Prescriber feedback will also be sought, and suggestions incorporated where appropriate. A "hits" counter will indicate the number of times the site is accessed. However, as it is only one strategy of many under the mantle of antimicrobial stewardship, it will be difficult to differentiate between the effect of this intervention and any others implemented.

6.2.4. Future developments

The author's hospital has committed to an electronic prescribing system in the medium term, and a System Requirements Specification has already been drafted. However, such a project would require substantial resources and planning and is not feasible at this point.

CPOE has the potential to improve antibiotic prescribing in many different ways. Some examples are given below:

(a) Alarms can indicate if a patient is allergic to a prescribed antibiotic.
(b) Alerts can indicate if a patient previously received that antibiotic or one from the same class.

(c) Order sets can be used to group antibiotic treatments along with C&S and other laboratory tests.
(d) Standard doses can be set as default. These can be absolute or tailored for the patient's age, weight or body surface area or even the infection type.
(e) Alerts can be used to indicate if a particular drug is restricted. Different antibiotics can have different levels of authorisation depending on the seniority of the doctor or their medical speciality.
(f) Automatic review dates can be incorporated for IV to oral switch. These can be links to laboratory parameters through rules.
(g) Automatic review dates can be incorporated for stop dates.
(h) Alerts can be integrated to guide dosing if blood levels are out of the desired range. Formulae-based pharmacokinetic calculators can be incorporated to calculate the revised dose.
(i) Alerts can be used to guide dosage if laboratory results indicate reduced liver or kidney function.
(j) Ordering a particular antibiotic can trigger an order for a laboratory test.
(k) An order for interacting drugs can be communicated to the prescriber through the form of an alert.
(l) Abnormal laboratory tests that are possibly due to a prescribed drug can be flagged for further investigation.
(m) Information to the user can be incorporated directly on screen or through links.

CPOE will also allow the accumulation of large amounts of prescribing data, which can be used for audit and research. Reports on antibiotic use can be generated and acted upon, daily, weekly, or at longer intervals as appropriate.

Of the commercially available antimicrobial CDS systems, TREAT and HELP would both require huge data input before becoming appropriate to the Irish setting. Both systems are resource intensive and would require significant ICT investment as well as significant ongoing human resources to configure and maintain them. Interoperability would also need to be examined: could either system integrate or interface easily with the existing laboratory systems or would they require replacement also? Are they more likely to operate in isolation? Realistically, their cost is prohibitive. Data mining the existing laboratory system and integration with CPOE appears to be a more practical and achievable solution in the medium to long term. In addition, CPOE also provides a more

patient safety-focussed approach to the use of all drugs, including antibiotics, than TREAT.

One of the problems with computerised CDS is the difficulty in interpreting the literature to establish the overall effect of CDS on patient morbidity and mortality. In the domain of infection, only HELP has shown a benefit in terms of and reduced LOS and reduced costs. No reduction in mortality has been demonstrated, and this is generally true for CDS. Although we know that CDS avoids incidents that could adversely affect the patient even to the point of avoiding death, it is difficult to establish that improvements in patient medication safety lead to a reduction in morbidity and mortality, standard end-points in any medical analysis.

6.2.5. Conclusion

This study has demonstrated that, in patients with an LRTI, who are admitted through the Emergency Department, there is poor compliance with the hospital's antimicrobial guidelines. This study proposes that provision of an electronic interactive form of the guidelines which is readily accessible, easy to use and clinically meaningful, has the potential to improve compliance with antimicrobial guidelines and reduce costs. This intervention, in the form of an electronic guideline in HTML, is to be implemented and assessed. In the future, the hospital will look further to electronic prescribing to improve the appropriateness and safety of prescribing in a more general manner, including for antibiotics.

7. Chapter 7: Conclusion

The use of antibiotics has been identified as an area where appropriate, accurate and targeted prescribing is vital for the recovery of the patient, minimisation of costs and reduction of the development of antibiotic resistant pathogens. CDS has the potential to support physicians and other healthcare professionals during the medication usage process. CDS may be computerised or non-computerised.

This study has built on a previous audit and demonstrated continued poor compliance with antibiotic guidelines in the author's hospital in the domain of lower respiratory tract infections, in patients admitted though the Emergency Department. The study has shown that patients were not prescribed antibiotics in a standard way; the under-treatment of these infections also emerged as a potential problem. Using the correct antibiotics by an appropriate route would have resulted in more doses of different antibiotics being used, but at a significantly lower overall cost per patient to the hospital.

The author performed an evaluation of the recent medical literature to identify the state-of-the-art in CDS in the domain of infection. Many different examples of CDS, both ICT-reliant and independent of ICT, were identified and evaluated. Having examined the examples of CDS applied in the domain of infection in the medical literature, the author chose a feasible example of a computerised CDS that could be easily implemented within existing ICT structures and clinical systems, as part of a broader package of interventions to improve antibiotic use. A prototype was developed and assessed for compliance with the critical factors for successful CDS. It scored 43 out of a possible 70, however the choice of intervention, and its design, were limited by the available resources.

The prototype CDS will be discussed with the microbiology team and users and the format agreed. Other pages will then be developed to cover all areas of infection and the prevention of infection, which will then be validated. It will be hosted on the hospital intranet and maintained by the specialist antibiotic pharmacist.

The uptake of the CDS will be assessed using a "hits" counter and also by repeating the DDD study post-implementation as part of the existing and ongoing programme of antibiotic audits.

It is hoped that individualised CDS will be possible when the hospital moves to an electronic prescribing system in the medium term.

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Appendices

Appendix A: Study Data Collection Form

Background

Patient initials _____ *MRN* _____

Age / DOB _____ *Admitting Consultant* _____

History of COPD Y N Antimicrobial drug allergy _____

On presentation

If LRTI (circle) Pneumonia noted COPD Other Not

If pneumonia (circle) Severe Not severe Not noted

Source on presentation Nursing home Community Hospital

Antimicrobials prescribed Y N

Exclusions

Microbiology consult Y N Cystic Fibrosis Y N

Antimicrobial drug use

Drug	*Route*	*Dose*	*No. doses*

Complaint with guidelines Y N Date completed ____/____/____

Appendix B: Defined Daily Doses (DDDs)

World Health Organisation, 2009

Name of drug	*DDD*	*Unit*	*Route*
Amoxicillin	1	Gram (g)	Oral
Amoxicillin	1	Gram (g)	Intravenous (IV)
Cefuroxime	3	Gram (g)	Intravenous (IV)
Clarithromycin	0.5	Gram (g)	Oral
Clarithromycin	1	Gram (g)	Intravenous (IV)
Co-amoxiclav	1 (of amoxicillin)	Gram (g)	Oral
Co-amoxiclav	3 (of amoxicillin)	Gram (g)	Intravenous (IV)
Levofloxacin	0.5	Gram (g)	Intravenous (IV)
Piperacillin / tazobactam	14 (piperacillin)	Gram (g)	Intravenous (IV)

Table 5: Table of Defined Daily Doses (WHO, 2009).

Name of drug	*Route*	*DDDs used*	*Cost per DDD*	*Total drug cost*
Amoxicillin	Oral	0	0.18	0
Amoxicillin	IV	0	1.56	0
Cefuroxime	IV	0.5	11.04	5.52
Clarithromycin	Oral	61.5	1.06	65.19
Clarithromycin	IV	1	22.98	22.98
Co-amoxiclav	Oral	101	0.86	86.96
Co-amoxiclav	IV	22	5.55	122.10
Levofloxacin	Oral	9	3.17	28.53
Piperacillin / tazobactam	IV	24.29	29.75	722.63
				1053.91

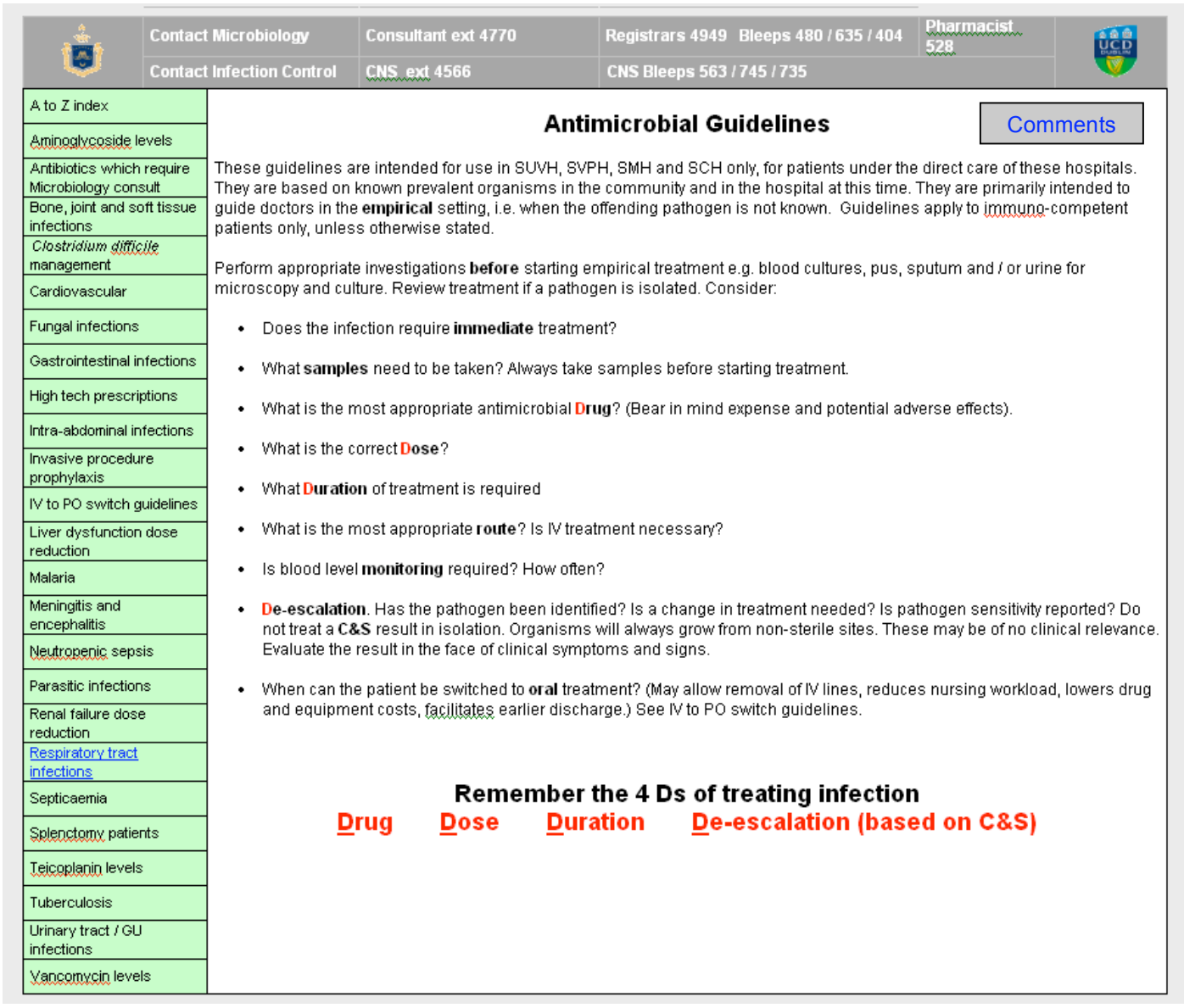
Table 6: Calculated amounts of administered DDDs and their cost in Euros (€).

Name of drug	*Route*	*DDDs used*	*Cost per DDD*	*Total drug cost*
Amoxicillin	Oral	15	0.18	2.70
Amoxicillin	IV	6	1.56	9.36
Cefuroxime	IV	0	11.04	0
Clarithromycin	Oral	119	1.06	126.14
Clarithromycin	IV	0	22.98	0
Co-amoxiclav	Oral	85.5	0.86	73.53
Co-amoxiclav	IV	27	5.55	149.85
Levofloxacin	Oral	0	3.17	0
Piperacillin / tazobactam	IV	12	29.75	357
				718.58

Table 7: Calculated amounts of guidelines DDDs and their cost in Euros (€).

Appendix C: HTML pages

(a) Home page



	Contact Microbiology	Consultant ext 4770	Registrars 4949 Bleeps 480 / 635 / 404	Pharmacist 528
	Contact Infection Control	CNS ext 4566	CNS Bleeps 563 / 745 / 735	

- A to Z index
- Aminoglycoside levels
- Antibiotics which require Microbiology consult
- Bone, joint and soft tissue infections
- *Clostridium difficile* management
- Cardiovascular
- Fungal infections
- Gastrointestinal infections
- High tech prescriptions
- Intra-abdominal infections
- Invasive procedure prophylaxis
- IV to PO switch guidelines
- Liver dysfunction dose reduction
- Malaria
- Meningitis and encephalitis
- Neutropenic sepsis
- Parasitic infections
- Renal failure dose reduction
- Respiratory tract infections
- Septicaemia
- Splenctomy patients
- Teicoplanin levels
- Tuberculosis
- Urinary tract / GU infections
- Vancomycin levels

Antimicrobial Guidelines

Comments

These guidelines are intended for use in SUVH, SVPH, SMH and SCH only, for patients under the direct care of these hospitals. They are based on known prevalent organisms in the community and in the hospital at this time. They are primarily intended to guide doctors in the **empirical** setting, i.e. when the offending pathogen is not known. Guidelines apply to immuno-competent patients only, unless otherwise stated.

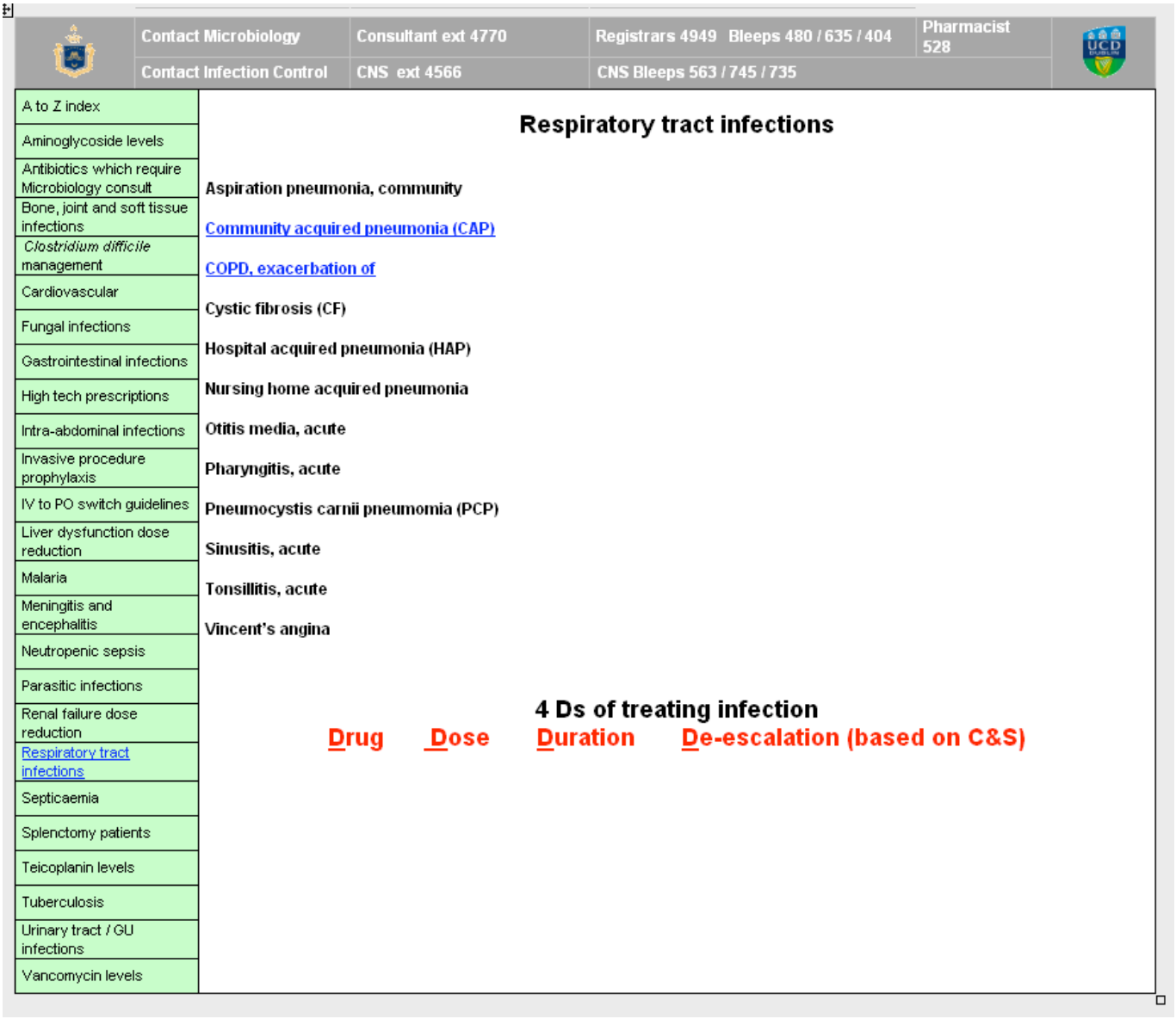
Perform appropriate investigations **before** starting empirical treatment e.g. blood cultures, pus, sputum and / or urine for microscopy and culture. Review treatment if a pathogen is isolated. Consider:

- Does the infection require **immediate** treatment?
- What **samples** need to be taken? Always take samples before starting treatment.
- What is the most appropriate antimicrobial **Drug**? (Bear in mind expense and potential adverse effects).
- What is the correct **Dose**?
- What **Duration** of treatment is required
- What is the most appropriate **route**? Is IV treatment necessary?
- Is blood level **monitoring** required? How often?
- **De-escalation**. Has the pathogen been identified? Is a change in treatment needed? Is pathogen sensitivity reported? Do not treat a **C&S** result in isolation. Organisms will always grow from non-sterile sites. These may be of no clinical relevance. Evaluate the result in the face of clinical symptoms and signs.
- When can the patient be switched to **oral** treatment? (May allow removal of IV lines, reduces nursing workload, lowers drug and equipment costs, facilitates earlier discharge.) See IV to PO switch guidelines.

Remember the 4 Ds of treating infection

Drug Dose Duration De-escalation (based on C&S)

(b) Respiratory tract infections page



	Contact Microbiology	Consultant ext 4770	Registrars 4949 Bleeps 480 / 635 / 404	Pharmacist 528
	Contact Infection Control	CNS ext 4566	CNS Bleeps 563 / 745 / 735	

- A to Z index
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- Septicaemia
- Splenctomy patients
- Teicoplanin levels
- Tuberculosis
- Urinary tract / GU infections
- Vancomycin levels

Respiratory tract infections

Aspiration pneumonia, community

Community acquired pneumonia (CAP)

COPD, exacerbation of

Cystic fibrosis (CF)

Hospital acquired pneumonia (HAP)

Nursing home acquired pneumonia

Otitis media, acute

Pharyngitis, acute

Pneumocystis carnii pneumomia (PCP)

Sinusitis, acute

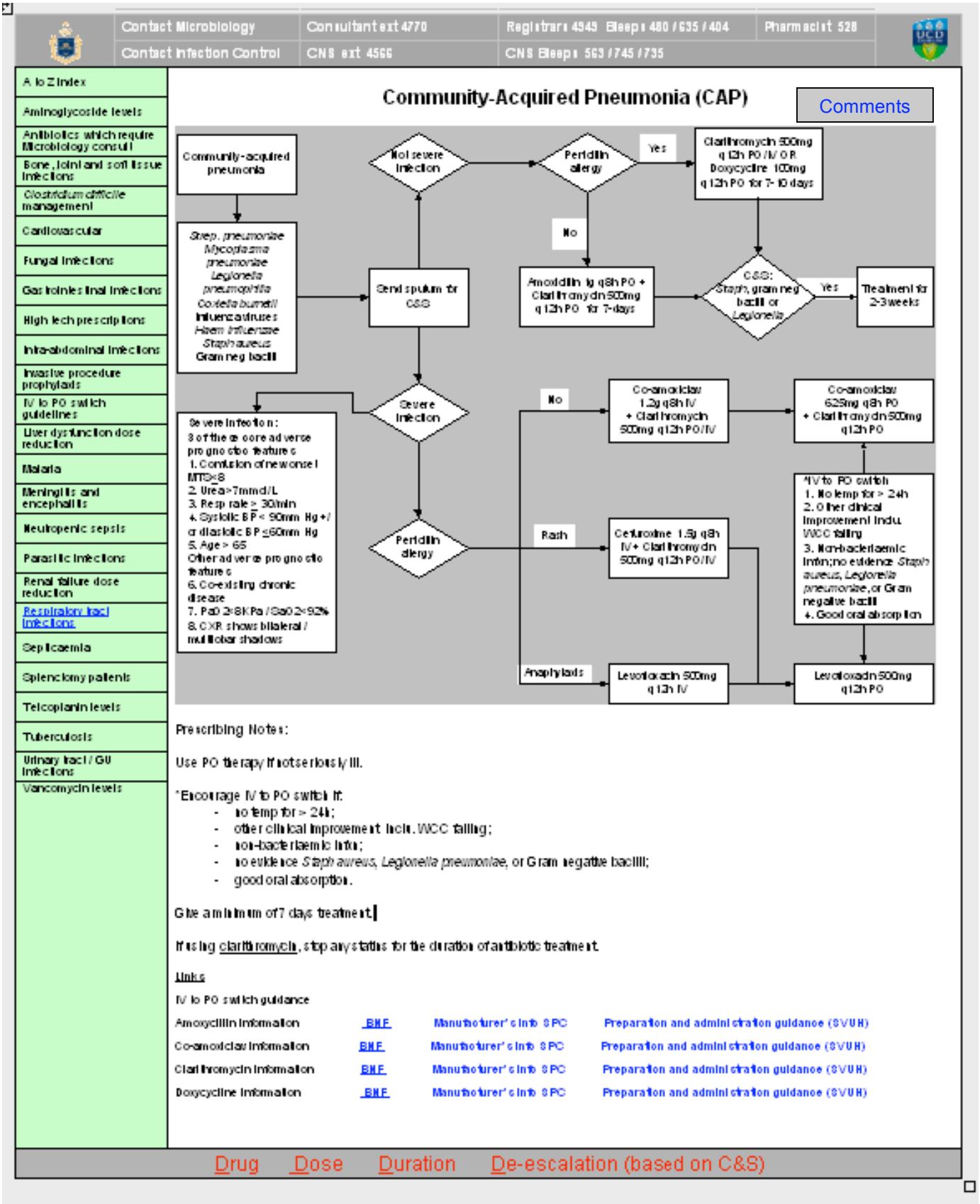
Tonsillitis, acute

Vincent's angina

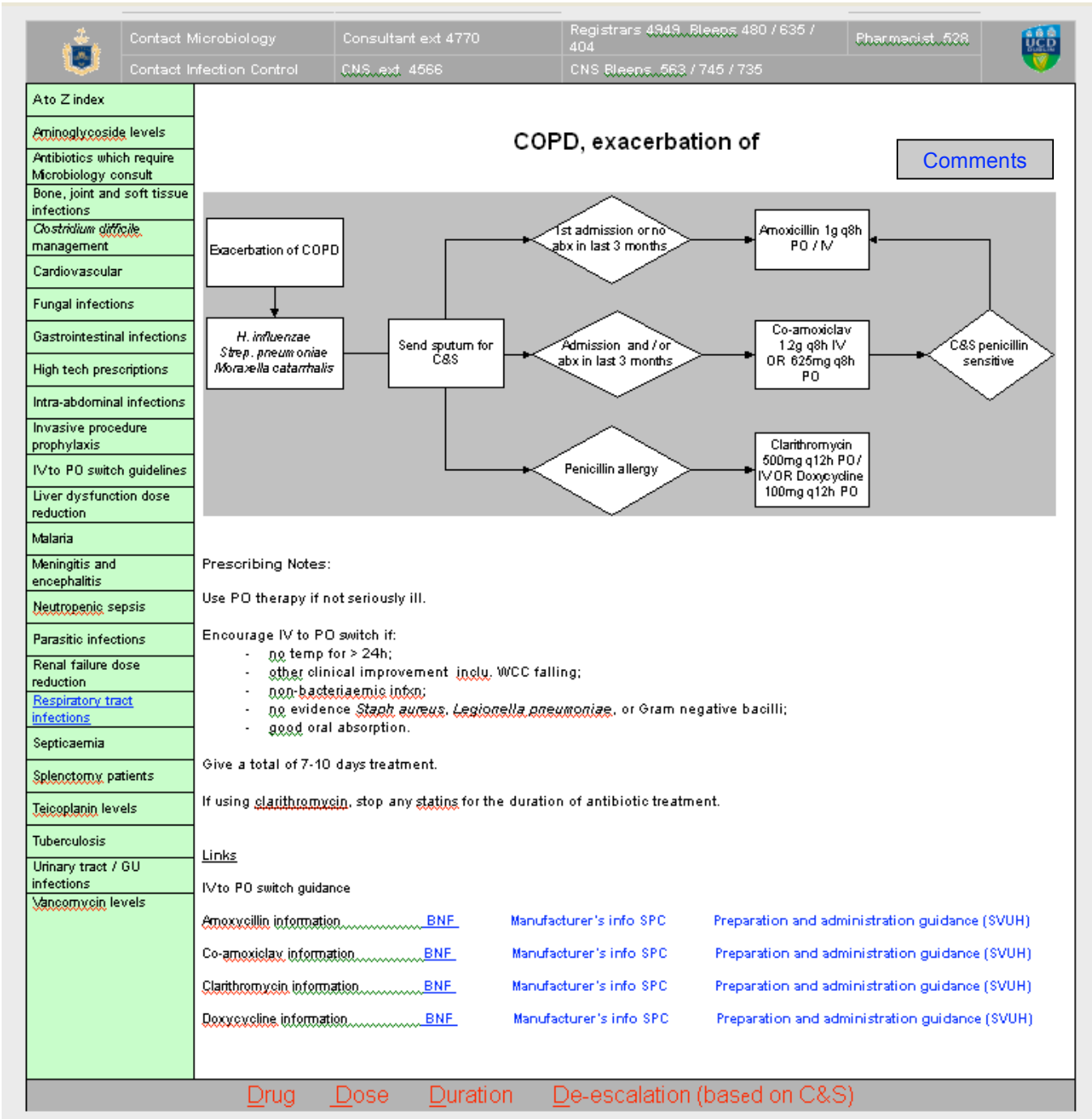
4 Ds of treating infection

Drug Dose Duration De-escalation (based on C&S)

(c) Community-acquired pneumonia page



(d) Chronic obstructive pulmonary disease page



Contact Microbiology | Consultant ext 4770 | Registrars 4949, Bleeps 480 / 635 / 404 | Pharmacist 528
Contact Infection Control | CNS ext 4566 | CNS Bleeps 563 / 745 / 735

A to Z index
Aminoglycoside levels
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Parasitic infections
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Respiratory tract infections
Septicaemia
Splenectomy patients
Teicoplanin levels
Tuberculosis
Urinary tract / GU infections
Vancomycin levels

COPD, exacerbation of

Comments

Prescribing Notes:

Use PO therapy if not seriously ill.

Encourage IV to PO switch if:

- no temp for > 24h;
- other clinical improvement inclu. WCC falling;
- non-bacteriaemic infxn;
- no evidence *Staph aureus*, *Legionella pneumoniae*, or Gram negative bacilli;
- good oral absorption.

Give a total of 7-10 days treatment.

If using clarithromycin, stop any statins for the duration of antibiotic treatment.

Links

IV to PO switch guidance

Amoxycillin information	BNF	Manufacturer's info SPC	Preparation and administration guidance (SVUH)
Co-amoxiclav information	BNF	Manufacturer's info SPC	Preparation and administration guidance (SVUH)
Clarithromycin information	BNF	Manufacturer's info SPC	Preparation and administration guidance (SVUH)
Doxycycline information	BNF	Manufacturer's info SPC	Preparation and administration guidance (SVUH)

Drug Dose Duration De-escalation (based on C&S)