Training Manual Appendix 2
MBIRA study: Guide to scoring appropriate-ness of antibiotic use by pathogen, including imputation of missing antibiotic susceptibilities

Contents

Excerpt from MBIRA Training Manual – Section 12

Section 12. Introduction to appropriate-ness of antibiotic use in MBIRA

One of the main research questions of the MBIRA study is to examine how the appropriate-ness of use of antibiotics, in terms of antibiotic drug being used, relates to outcomes for the patient.

There are many different aspects of whether antibiotic use is appropriate, including

1. *Suitable antibiotic drug for empirical treatment of an infection "syndrome" in a certain age group*
2. *Suitable antibiotic drug for an identified bacterial pathogen, based on antibiotic resistance tests*
3. *Suitable dosing of antibiotic drug for this patient, based on their weight, renal function, other factors*
4. *Suitable route of administration of antibiotic drug – intra-venous versus oral versus other*
5. *Suitable timing of the first (and subsequent) doses of antibiotics from onset of illness*
6. *Suitable duration of antibiotic use, in terms of overall number of days of (effective) therapy*
7. *Suitable choice of agent, based on local availability, costs, antibiotic usage guidelines/policies*

And probably there are several other factors too! We are not able to assess all of these in this study, but we are going to focus on aspects "2", with some attention also to aspects "3", "6" and "7". We are therefore particularly looking at just the question of whether the antibiotic agent being used would be expected to be active against the specific bacteria identified from the positive blood culture.

In order to do this, one or two experienced people (→ see below) in each site need to assess each antibiotic used for each patient with bacteraemia to say whether or not, in terms of the local antibiotic susceptibility testing results, this antibiotic would be expected to be active against this particular bacteria.*

This is obviously a very narrow interpretation of the "appropriate-ness" of antibiotic use – patients might receive an "appropriate" choice of drug agent, but at an inadequate (or excessive) dose or via an inappropriate route or at an excessive cost to the hospital or patient. Drugs might have passed their expiry date or not be administered appropriately. The patient might miss some doses of an appropriate antibiotic due to limited availability or oversight by treating staff. Also, there may be some antibiotic drugs used where there is no local testing information available to determine whether or not the agent is likely to be effective. Furthermore, for some types of antibiotic resistance (eg resistance mediated by ESBL enzymes), there are differences of opinion amongst microbiologists over whether or not particular antibiotic agents are "appropriate" to use, though current versions of major antibiotic susceptibility testing guidelines (EUCAST and CLSI) now make broad recommendations on interpretation of test results in most situations.

For the purposes of this study, we are just going to focus on this narrow question relating to aspect number "2" above – ***does this particular drug potentially have therapeutic activity against this particular bacteria?*** *This will mean each drug will typically need a "yes" or "no" answer each day to say whether the relevant person/people considers this to be an appropriate drug to use. We will also allow options for "unable to determine" and "Yes, but at inadequate dosing" to be used. All of these choices will be based on the professional opinion of the relevant person. The next section describes how to enter this information.*

** In each site, an appropriate person with extensive clinical and microbiological experience should be making this assessment for "appropriate-ness" of antibiotic drug choice all the patients in the study – this assessment should not be performed by a study research nurse in isolation. Typically, this person will be the site lead or another clinical microbiologist and will participate in further relevant study trainings. The choice of who will perform this part of the study should be agreed in advance with the study co-ordinators.*

Purpose of this guide

This guide is intended to support a standardized approach to recording the "appropriate-ness" of antibiotic use in the MBIRA study, as a supplementary training material to the MBIRA study Training Manual. This guide includes some general information, a flow-chart for step-by-step performance of this scoring, 5 training cases, some Frequency Asked Questions and an Appendix of Rules of Imputing (=inferring) antibiotic resistance results for additional antibiotics.

One (or at most two) individual(s) in each site of the MBIRA study should be responsible for reading this guide, including doing the training cases, and scoring the "appropriate-ness" of antibiotic use.

General principles and Terminology

We have used the term "appropriate-ness" for this document, but it may be more helpful to think of this work in terms of "**effectiveness**" or "**activity**" of antibiotics. What we are attempting to record is whether or not the particular antibiotic agent was, in retrospect, actually "effective" or "active" against the specific infecting bacteria, based on the full laboratory results. The clinicians treating the patient at start of the patient's illness would not have had access to this information, so they may have inadvertently used ineffective antibiotic agents, or not have given any antibiotics at all. We are not trying to make any judgement about whether those clinicians made a right or wrong decision, just to determine if, in retrospect, the drugs should have been effective.

When considering whether the antibiotics used for patients in the MBIRA study were, in retrospect, active against the isolated bacteraemia pathogen, we will assess each individual pathogen-antibiotic combination separately using the locally-reported antibiotic susceptibilities, as available. **As a general principle, we will normally directly follow the results of the in-vitro susceptibility testing,** so long as these appear consistent with the bacterial species identified.

Individual institutions differ on which drugs are used for susceptibility testing, though the majority of sites are following the CLSI guidelines for interpretation. This guide uses the following abbreviations

R = Resistant
S = Susceptible (also sometime used to abbreviate for "sensitive")
I = Intermediate

For simplicity, we will always consider "Intermediate" (or alternatively "Area of Therapeutic Uncertainty") susceptibility results as being "resistant".

All susceptibility testing will be repeated at the MBIRA study Reference Laboratory in South Africa at the end of the study. Therefore, bacterial isolates from bacteraemia cases where the patients were enrolled into the MBIRA study must be saved in a suitable freezer until the end of the study (end of 2021 / early 2022) and then will be sent to the reference laboratory.

Dosing

As far as the dose of antibiotics used is concerned, our general principle will be to follow dosing recommendations for antibiotics as described in the British National Formulary (BNF) for adults and the British National Formulary-Children (BNF-C) as appropriate for age of patient. Ideally, we will use the most recent information available, but the BNF website does not normally allow access if you are outside of the UK. We have pdf versions for 2018-19 editions (in Dropbox folder) – it seems unlikely there are substantial changes in dosing for these drugs in the past year. For patients with known renal impairment, we will also refer to the Renal Drug Handbook (3rd Edition) for specialist dosing recommendations. So long as the dose of antibiotic recorded to be administered in a 24 hour period falls within the recommended range of dosing for the antibiotic described for the particular patient circumstances, we will consider this as "appropriate" antibiotic treatment. The patient does not have to be on the "maximum" allowable dose of a particular agent, just within the recommended dose range for the relevant route of administration.

Where there are known to be special circumstances for the particular patient (eg. under-weight or overweight, acute or chronic renal impairment) that affect the dosing, we will consider the dosing as "appropriate" if the relevant circumstances are described in the BNF, BNF-C or Renal Drug Handbook.

British National Formulary	https://bnf.nice.org.uk/ OR 2018-19 pdf version in Dropbox folder
British National Formulary – Children	https://bnfc.nice.org.uk/ OR 2018-19 pdf version in Dropbox folder
Renal Drug Handbook (3rd Edition)	pdf version available in MBIRA study Dropbox folder

Imputation rules

In some cases, the susceptibilities to specific antibiotics that were actually used may not be listed in local susceptibility reports – in several MBIRA study sites, a wider range of antibiotics is used than is routinely tested in the laboratory. We do not expect any additional susceptibility testing to be performed in the participating laboratories, so sometimes, it may not be possible to determine if the antibiotic used would or would not have been effective against the infecting bacteria. However, sometimes the response of particular bacteria to certain antibiotics can be predicted ("**imputed**") based on general microbiological principles or known susceptibility results of other antibiotics.

We therefore have created a set of rules to impute some further antibiotic susceptibilities using microbiologic principles and knowledge of the spectrum of likely activity for each antibiotic-pathogen combination – this is given in Appendix 1. A "key" to the abbreviations used in these imputations is shown at the start if the Appendix, followed by the general and species-specific rules. Not all antibiotic sensitivities can be imputed – in some cases it will be impossible to determine "appropriate-ness" without a relevant test being performed.

There are some circumstances relating to the interpretation of 3rd generation cephalosporin (3GC) antibiotic susceptibility (based on particular mechanisms of resistance) where there is some degree of uncertainty about interpretation. In Appendix 2, we describe some additional sub-group analyses that we will perform at the end of the study to allow for different inferences from particular mechanisms of resistance.

Practical work

For entering this information into the Redcap database, this recording of information needs to be done for each drug on a day-by-day basis – this is a bit repetitive, but it allows for changes of drug doses each day. We suggest that these information are completed at each site on a monthly basis – we estimate it make take an individual 1-2 hours to complete all the information for all the MBIRA patients in a month.

We recommend that this work is done by 1 or 2 individuals at each MBIRA site. Ideally this work should be staff with a professional training as a clinical microbiologist or as an experienced clinician. In some situations, there may be an element of judgement to make about these interpretations – if there is uncertainty these can be discussed with the MBIRA lead investigators (Alexander Aiken alexander.aiken@lshtm.ac.uk and Andrew Whitelaw awhitelaw@sun.ac.za) if needed.

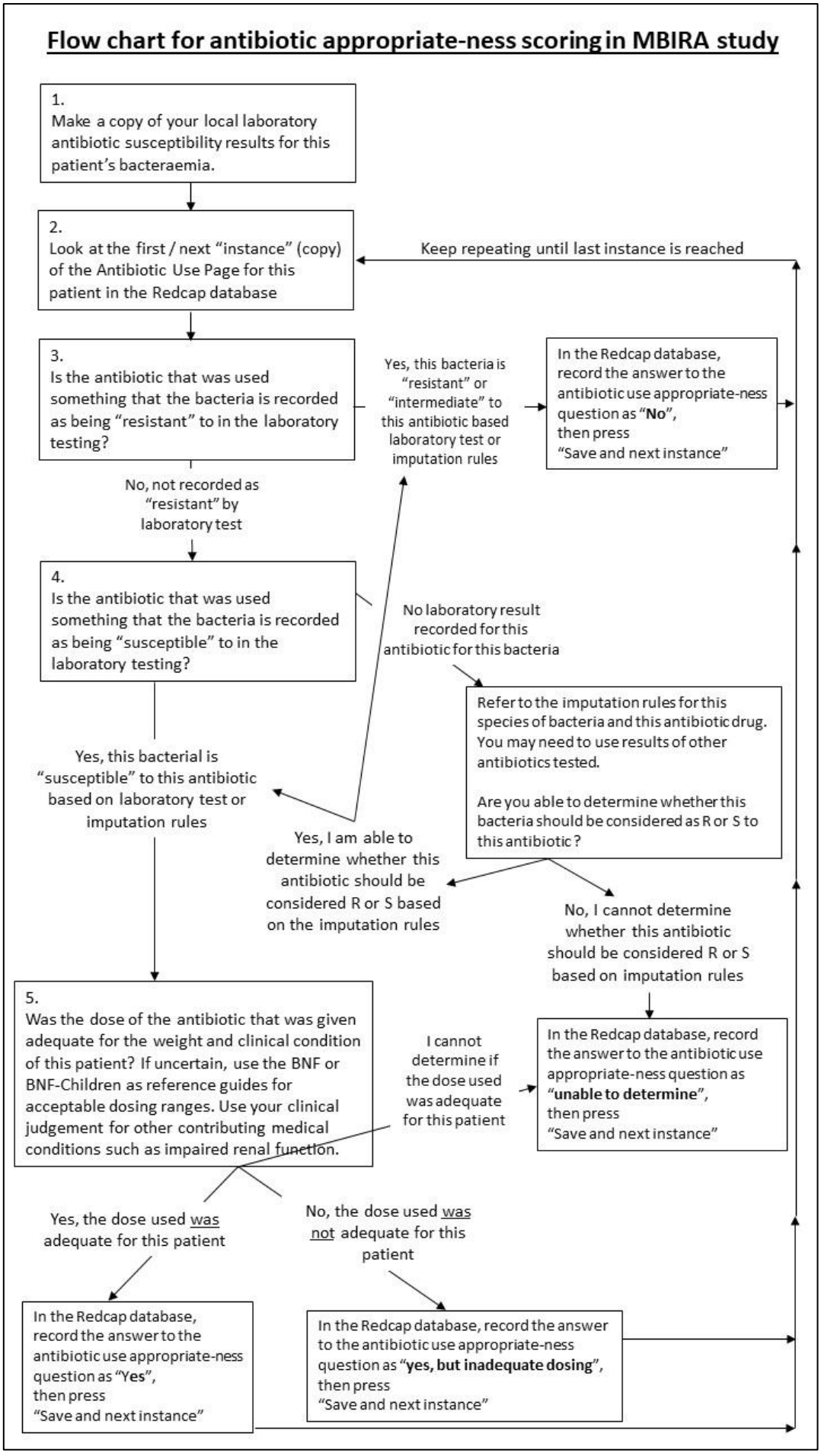
** Now read text in Section 12 of MBIRA Training Manual on "Training exercise 4 – coding appropriate-ness of antibiotic use in MBIRA" – this illustrates how the RedCap interface is used **

As further materials to try to make this process easier, please see the following

- Flow chart for antibiotic appropriate-ness scoring process
- 5 example cases for practicing this scoring
- Frequently Asked Questions

The full imputation rules for the MBIRA study are provided in Appendix 1.

The further planned analyses are detailed in Appendix 2.


Flow chart for antibiotic appropriate-ness scoring in MBIRA study
1.
Make a copy of your local laboratory antibiotic susceptibility results for this patient's bacteraemia.
2.
Look at the first / next "instance" (copy) of the Antibiotic Use Page for this patient in the Redcap database
Keep repeating until last instance is reached
3.
Is the antibiotic that was used something that the bacteria is recorded as being "resistant" to in the laboratory testing?
Yes, this bacteria is "resistant" or "intermediate" to this antibiotic based laboratory test or imputation rules
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "No", then press "Save and next instance"
No, not recorded as "resistant" by laboratory test
4.
Is the antibiotic that was used something that the bacteria is recorded as being "susceptible" to in the laboratory testing?
No laboratory result recorded for this antibiotic for this bacteria
Refer to the imputation rules for this species of bacteria and this antibiotic drug. You may need to use results of other antibiotics tested.
Are you able to determine whether this bacteria should be considered as R or S to this antibiotic ?
Yes, this bacterial is "susceptible" to this antibiotic based on laboratory test or imputation rules
Yes, I am able to determine whether this antibiotic should be considered R or S based on the imputation rules
No, I cannot determine whether this antibiotic should be considered R or S based on imputation rules
5.
Was the dose of the antibiotic that was given adequate for the weight and clinical condition of this patient? If uncertain, use the BNF or BNF-Children as reference guides for acceptable dosing ranges. Use your clinical judgement for other contributing medical conditions such as impaired renal function.
I cannot determine if the dose used was adequate for this patient
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "unable to determine", then press "Save and next instance"
Yes, the dose used was adequate for this patient
No, the dose used was not adequate for this patient
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "Yes", then press "Save and next instance"
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "yes, but inadequate dosing", then press "Save and next instance"

Training cases for recording antibiotic appropriateness

These are 5 fictitious cases created to illustrate some of the difficulties of recording this antibiotic appropriate-ness information. The MBIRA study site lead for this aspect of the study should work through these to check they are familiar with the recommended approach, even if they are an experienced clinical microbiologist. Fill in the column titled "Was this antibiotic appropriate" using the options from the box at the bottom of the page.

Training Case 1

Bacteraemia details	
Bacteria identified	E. coli
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	S
Ciprofloxacin	R
Ceftriaxone	S
Amikacin	S
Co-trimoxazole	S

Patient details	
Age	5 yrs
Weight	16.0 kg
Other medical conditions	Nil known
Outcome	Patient discharged on day 4 of treatment, to go home with an oral antibiotic for 7 days

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	400 mg	iv	4	
0	Gentamicin	40 mg	iv	2	
1	Ampicillin	400 mg	iv	6	
1	Gentamicin	40 mg	iv	3	
2	Ampicillin	400 mg	iv	6	
2	Gentamicin	40 mg	iv	1	
3	Ceftriaxone	1200 mg	iv	1	
3	Gentamicin	40 mg	iv	3	
4	Ceftriaxone	1200 mg	iv	1	
4	Gentamicin	40 mg	iv	1	
4	Co-trimoxazole	240 mg	po	2	
5	Co-trimoxazole	240 mg	po	2	
6	Co-trimoxazole	240 mg	po	2	
7	Co-trimoxazole	240 mg	po	2	
8	Co-trimoxazole	240 mg	po	2	
9	Co-trimoxazole	240 mg	po	2	
10	Co-trimoxazole	240 mg	po	2	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 1.

1. For this child, you may need to check what the recommended doses are for these drugs based on the child's weight – you can look these up, if you need, in the BNF-Children.
2. Day 0 = the day that the blood culture was taken. In most cases, this will also be the day that antibiotic treatment is started, though sometimes a patient will already be on antibiotics before this day. For example, the patient may have been admitted to hospital in the afternoon, so it may only have been possible to give 1-2 doses of some of the multi-dose medications that day. Therefore, on Day 0, the patient may often not receive the full number of doses in a 24 hour period that would be recommended. Do not score this day as "inadequate dosing" as there may not have been sufficient time for full number of doses to be given.
3. Similar to note 1 above, on a day that a patient leaves hospital (or dies), there may not be time in that 24 hour period to receive all the recommended doses of antibiotic treatment. Again, do not score this an "inadequate dosing of antibiotic" as the patient may not have been available to receive the full number of doses, or there may have been a change of prescription.
4. Similar to notes 1 and 2, the same situation may apply on any day when a patient changed antibiotic treatments. Again, for any other day where the antibiotics are stopped or started, do not consider these days as inadequate dosing.
5. Apart from Day 0 and the day the patient left hospital, for one day of one of the antibiotics treatments in the example above, this patient did not receive an "adequate" dosing of the drug, according to the British National Formulary for Children. Did you identify which drug on which day this was ? Hint: look at the number of doses of Gentamicin given on Day 4.
6. When patients are discharged home with an oral antibiotic treatment, it is very difficult to determine their compliance to this treatment. Therefore, only assess whether the antibiotic would have been appropriate for treating this bacteria – we cannot assess whether this drug was actually taken.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	400 mg	iv	4	No
0	Gentamicin	40 mg	iv	2	Yes
1	Ampicillin	400 mg	iv	6	No
1	Gentamicin	40 mg	iv	3	Yes
2	Ampicillin	400 mg	iv	6	No
2	Gentamicin	40 mg	iv	1	Yes, but inadequate dosing
3	Ceftriaxone	1200 mg	iv	1	Yes
3	Gentamicin	40 mg	iv	3	Yes
4	Ceftriaxone	1200 mg	iv	1	Yes
4	Gentamicin	40 mg	iv	1	Yes, but inadequate dosing
4	Co-trimoxazole	240 mg	po	2	Yes
5	Co-trimoxazole	240 mg	po	2	Yes
6	Co-trimoxazole	240 mg	po	2	Yes
7	Co-trimoxazole	240 mg	po	2	Yes
8	Co-trimoxazole	240 mg	po	2	Yes
9	Co-trimoxazole	240 mg	po	2	Yes
10	Co-trimoxazole	240 mg	po	2	Yes

Training Case 2

Bacteraemia details	
Bacteria identified	K .pneumoniae
Drugs reported	Laboratory result
Gentamicin	R
Ciprofloxacin	R
Ceftriaxone	R
Amikacin	S
Meropenem	S

Patient details	
Age	56 yrs
Weight	73.5 kg
Other medical conditions	Nil known
Outcome	Patient died on day 4

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Ciprofloxacin	500 mg	po	2	
0	Ciprofloxacin	500 mg	Po	1	
0	Ampicillin	1000 mg	iv	2	
0	Gentamicin	250 mg	iv	1	
1	Ceftriaxone	1000 mg	iv	1	
1	Gentamicin	250 mg	iv	3	
2	Ceftriaxone	1000 mg	iv	1	
2	Gentamicin	250 mg	iv	3	
3	Ceftriaxone	1000 mg	iv	1	
3	Amikacin	540 mg	iv	3	
4	Imipenem	1000 mg	iv	3	
4	Amikacin	540 mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 2

1. For this adult, you may need to check what the recommended doses are for these drugs based on the patient's weight – you can look these up, if you need, in the BNF.
2. This is a more extensively antibiotic-resistant bacteria, so much more of the antibiotic treatment is not appropriate or "not effective". Only the amikacin and meropenem drugs are effective here.
3. This patient was already on antibiotic treatment at the time the blood culture was taken. There is a drug treatment recorded for "Day -1" – this means this drug was being given the day before the blood culture was taken.
4. For the ampicillin (which is effectively the same drug as amoxicillin) and the imipenem antibiotics, you need to look these antibiotics up in the "imputation rules" later in Appendix 1 of this Guide. Some bacteria are inherently resistant to certain antibiotics, so the laboratory may not bother to test these drugs.
5. Note that gentamicin and amikacin (both are aminoglycoside drugs) can be dosed as once daily, twice daily or three times daily regimens, but with different drug amounts for each different regime. In many African countries, multiple daily doses (typically 3 times daily) is preferred – this can achieve suitable treatment levels.
6. Note that the patient died on Day 4 – so do not score the antibiotic treatment on this day as "inadequate dosing", as there was not necessarily time available to receive this drug.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Ciprofloxacin	500 mg	po	2	No
0	Ciprofloxacin	500 mg	Po	1	No
0	Ampicillin	1000 mg	iv	2	No
0	Gentamicin	250 mg	iv	1	No
1	Ceftriaxone	1000 mg	iv	1	No
1	Gentamicin	250 mg	iv	3	No
2	Ceftriaxone	1000 mg	iv	1	No
2	Gentamicin	250 mg	iv	3	No
3	Ceftriaxone	1000 mg	iv	1	No
3	Amikacin	540 mg	iv	3	Yes
4	Imipenem	1000 mg	iv	3	Yes
4	Amikacin	540 mg	iv	1	Yes

Training Case 3

Bacteraemia details	
Bacteria identified	Proteus vulgaris
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	R
Ciprofloxacin	S
Cefotaxime	R
Amikacin	S
Co-amoxiclav	R

Patient details	
Age	1 year and 4 months
Weight	10.2 kg
Other medical conditions	Nil known
Outcome	Discharged on Day 8

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	250 mg	iv	4	
0	Gentamicin	25 mg	iv	3	
0	Vancomycin	100 mg	iv	3	
1	Ceftriaxone	500 mg	iv	1	
1	Amikacin	75 mg	iv	2	
1	Vancomycin	100 mg	Iv	4	
2	Ceftriaxone	500 mg	iv	1	
2	Amikacin	75 mg	iv	2	
3	Meropenem	100 mg	iv	1	
3	Amikacin	75 mg	iv	2	
4	Amikacin	75 mg	iv	2	
5	Amikacin	75 mg	iv	1	
6	Amikacin	75 mg	iv	2	
7	Amikacin	75 mg	iv	2	
8	Amikacin	75 mg	iv	2	
9	Amikacin	75 mg	iv	2	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 3

1. Note that the laboratory testing here is performed with the antibiotic Cefotaxime, but the patient is treated with Ceftriaxone. You may need to look up in the "imputation rules" in Appendix 1 to check how to interpret the susceptibility status for Ceftriaxone.

2. The Research nurse has recorded the use of the Drug "Vancomycin" for this patient. Look up in the "imputation rules" to see which antibiotic drugs have no effective activity against the Gram-negative bacteria that we are studying in MBIRA. You could give feedback to the study nurse that it is not necessary to record the use of drugs that have no activity against Gram-negative bacteria

3. This patient received a single dose of treatment with drug "meropenem" on Day 3. Are you able to use the imputation rules for this species to determine if this drug would have been effective ? What do you think of the dosing received here, bearing in mind that this drug is started (and stopped) on this day ?

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	250 mg	iv	4	No
0	Gentamicin	25 mg	iv	3	No
0	Vancomycin	100 mg	iv	3	No
1	Ceftriaxone	500 mg	iv	1	No
1	Amikacin	75 mg	iv	2	Yes
1	Vancomycin	100 mg	Iv	4	No
2	Ceftriaxone	500 mg	iv	1	No
2	Amikacin	75 mg	iv	2	Yes
3	Meropenem	100 mg	iv	1	Yes, but inadequate dosing*
3	Amikacin	75 mg	iv	2	Yes
4	Amikacin	75 mg	iv	2	Yes
5	Amikacin	75 mg	iv	1	Yes, but inadequate dosing
6	Amikacin	75 mg	iv	2	Yes
7	Amikacin	75 mg	iv	2	Yes
8	Amikacin	75 mg	iv	2	Yes
9	Amikacin	75 mg	iv	2	Yes

* In practice, if a drug was just given for a single dose in this way, it would be difficult to say whether or not the agent was dosed adequately – the drug may and been started and stopped on the same day. We are trying to gain consistency across the study sites, but this will be difficult in some situations.

Please make your best judgements and seek advice as needed.

Training Case 4

Bacteraemia details	
Bacteria identified	E.coli
Drugs reported	Laboratory result
Amoxicillin	R
Gentamicin	S
Ciprofloxacin	R
Cefotaxime	R
Amikacin	S
Ceftazidime	R
Co-amoxiclav	R
Co-trimoxazole	R
Imipenem	S
Chloramphenicol	S

Patient details	
Age	9 days
Weight	1.9kg
Other medical conditions	Prematurity (born 34/40)
Outcome	Completed treatment, discharged from hospital 6 weeks after completing antibiotic treatment

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	60 mg	iv	3	
0	Flucloxacillin	50mg	iv	3	
0	Gentamicin	10 mg	iv	1	
1	Co-amoxiclav	60 mg	iv	2	
1	Gentamicin	10 mg	Iv	1	
2	Co-amoxiclav	60 mg	iv	2	
2	Gentamicin	10 mg	iv	1	
3	Gentamicin	10 mg	iv	1	
4	Meropenem	40 mg	iv	3	
5	Meropenem	40 mg	iv	3	
6	Meropenem	40 mg	iv	3	
7	Meropenem	40 mg	iv	3	
8	Meropenem	40 mg	iv	3	
9	Meropenem	40 mg	iv	3	
10	Meropenem	40 mg	iv	3	
11	Meropenem	40 mg	iv	3	
12	Meropenem	40 mg	iv	3	
13	Meropenem	40 mg	iv	3	
14	Meropenem	40 mg	iv	3	
15	Meropenem	40 mg	iv	3	
16	Meropenem	40 mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 4

1. For the antibiotics Flucloxacillin and Meropenem, you may need to look at the "imputation rules" in Appendix 1.

2. Not that amoxicillin and ampicillin are, in microbiological terms, equivalent drugs, so the susceptibility testing results for these two are interchangeable. The only different in pharmacological terms is that amoxicillin is water soluble, so the drug can be taken orally.

3. What do you think about the duration of treatment with the antibiotic Meropenem ? Typically, Gram-negative bloodstream infections need only 7-10 days antibiotic treatment, so long as there has been adequate "source control" of any focus of infection (such as an abscess or gastro-intestinal perforation). So, the duration of the treatment for this patient may be excessively long. However, making a judgment on the duration of treatment is not the purpose of our evaluation here – you just need to decide if the antibiotic is "effective" against the bacterial causing the bloodstream infection.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	60 mg	iv	3	No
0	Flucloxacillin	50mg	iv	3	No
0	Gentamicin	10 mg	iv	1	Yes
1	Co-amoxiclav	60 mg	iv	2	No
1	Gentamicin	10 mg	Iv	1	Yes
2	Co-amoxiclav	60 mg	iv	2	No
2	Gentamicin	10 mg	iv	1	Yes
3	Gentamicin	10 mg	iv	1	Yes
4	Meropenem	40 mg	iv	3	Yes
5	Meropenem	40 mg	iv	3	Yes
6	Meropenem	40 mg	iv	3	Yes
7	Meropenem	40 mg	iv	3	Yes
8	Meropenem	40 mg	iv	3	Yes
9	Meropenem	40 mg	iv	3	Yes
10	Meropenem	40 mg	iv	3	Yes
11	Meropenem	40 mg	iv	3	Yes
12	Meropenem	40 mg	iv	3	Yes
13	Meropenem	40 mg	iv	3	Yes
14	Meropenem	40 mg	iv	3	Yes
15	Meropenem	40 mg	iv	3	Yes
16	Meropenem	40 mg	iv	1	Yes

Training Case 5

Bacteraemia details	
Bacteria identified	K .pneumoniae
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	S
Ciprofloxacin	R
Amikacin	S
Cefotaxime	S
Imipenem	S
Co-trimoxazole	R

Patient details	
Age	72 yrs
Weight	82.9 kg
Other medical conditions	HIV+, advanced disease Renal failure, on haemodialysis x 3 weekly
Outcome	Patient died on day 3

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Co-trimoxazole	480mg	po	1	
0	Ceftriaxone	500 mg	iv	1	
0	Co-trimoxazole	480mg	po	1	
1	Ceftriaxone	500 mg	iv	1	
1	Gentamicin	80 mg	iv	1	
2	Ceftriaxone	1000 mg	iv	2	
2	Meropenem	500 mg	iv	1	
3	Meropenem	1000mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 5.

1. Note that this is a patient with known chronic renal impairment and on 3 x weekly haemodialysis, so you may need to check the dosing details in the Renal Drug Handbook, available in the MBIRA study Dropbox folder. Some of the recommended dosing changes are surprising, so always worth checking for patients with renal disease.

2. You many need to check the imputation rules for the drugs “meropenem” and “ceftriaxone” – these are not the same drugs that the laboratory report describes.

3. This is an HIV+ patient who is receiving oral co-trimoxazole on Day -1 and Day 0, mostly likely as long term prophylaxis. If a research nurse records other specialist medications in the MBIRA database (eg anti-retroviral or anti-TB drugs) that have no activity against enterobacteria, you should make sure that you let them know that this is not needed for this study. Co-trimoxazole (and some quinolone drugs used for treating TB) can have activity against Gram-negative bacteria, so should be recorded.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Co-trimoxazole	480mg	po	1	No
0	Ceftriaxone	500 mg	iv	1	Yes, but inadequate dosing
0	Co-trimoxazole	480mg	po	1	No
1	Ceftriaxone	500 mg	iv	1	Yes, but inadequate dosing
1	Gentamicin	80 mg	iv	1	Yes, but inadequate dosing
2	Ceftriaxone	1000 mg	iv	2	Yes
2	Meropenem	500 mg	iv	1	Yes
3	Meropenem	1000mg	iv	1	Yes

Frequently Asked Questions

1. **What should I do if there are more than one bacteria recorded in the blood culture – for example 1 x E.coli (with very few drug resistances) and 1 x K. pneumoniae (with more extensive drug resistance) ? What about if one of the bacteria in the blood culture is thought to be a skin contaminant ?**

Response: When there are multiple different bacteria in the blood culture, you should only give responses to the "appropriate-ness" questions for the Enterobacteria isolated. So, if there are other non-enterobacteria pathogens (eg. S. aureus, Strep. penumoniae or Pseudomonas aeruginosa) or likely contaminating bacteria (eg. Coagulase-negative staphylococci, bacillus spp. , micrococcus spp.), you should ignore these.

If there are two (or more) separate Enterobacteria in the same blood culture, this is more difficult. The best approach is to consider what is the "worst case" scenario of treatment across the different identified organisms – so if one bacteria is Resistant and the other is Susceptible for a particular antibiotic, then to use the "resistant" result when considering the appropriate-ness of the particular antibiotic.

2. **What should I do if the dose of the antibiotic given seems <u>excessively high</u> for the patient, either based on their weight or other medical conditions ?**

Response: excessively high dosing is a different aspect of "appropriate-ness" that we are not assessing in this study, so no need to record this – you should just indicate whether or not this drug was effective against the particular bacteria in this patient. However, if you notice that this is a frequent occurrence and you think that patients may be at risk, this information/concern should certainly be fed back to ward-based clinicians and/or pharmacists.

3. **If the dosing of the medication for the patient seems to be consistently too low, but there is no medical explanation for this, what should I do ?**

Response: it is possible that there are some clinical details for this patient that have not been captured by the MBIRA study form or the research nurse has recorded incorrectly (eg wrong weight). If you have concerns about the dosing for medications, it would be prudent to speak to the research nurse about the case or to review the medical records for this patient directly.

Appendix 1 : Full imputation rules

Key for abbreviations

Imputation abbreviation	Explanation
R	This means that the organism will always be considered to be resistant to the antibiotic. (R = Resistant). *Example: vancomycin for Klebsiella spp. will always be considered as a non-active antibiotic.*
S	This means the organism will always be considered as susceptible to the antibiotic. (S= Susceptible). There are no examples of this situation for the Enterobacterales bacteria.
E	This means Equals, meaning that the susceptibility for this antibiotic is considered equivalent to the result for a different antibiotic. *Example: For E.coli, "E meropenem" for doripenem means that if doripenem susceptibility is missing, but meropenem is reported as susceptible, then doripenem can be considered to be susceptible too.*
If missing then "rule(s) for alternate antibiotic"	This means that if the susceptibility for the antibiotic of interest is missing, then the algorithm looks at the next part of the rule and applies that. These further follow a hierarchial order; *For example, for ceftriaxone: "if missing then E cefotaxime; if missing then E cefpodoxime; else ." This means the algorithm first looks to see if there is susceptibility reported for cefotaxime; if missing, then the algorithm looks for susceptibility for cefpodoxime, if that is also missing, then the result is considered as missing.*
If missing then .	This means that if the susceptibility to the antibiotic is missing (note that missing is typically recorded in a database as "."), then the algorithm will list that particular antibiotic-organism combination as missing (because an imputation could not be reliably performed). In this case, if an antibiotic was used and the susceptibility status is "missing", then the "appropriateness" of that antibiotic use should be recorded as "unable to determine"
If missing then R	This means that the algorithm will report the organism to be resistant to the antibiotic if the susceptibility is missing. This is used when the organism is typically, but not always, resistant to this agent.

Agents always considered as inactive against all Enterobacterales

Antibiotic	**Susceptibility imputation**
Clindamycin	R
Flucloxacillin / Oxacillin / Cloxacillin / Nafcillin	R
Linezolid	R
Metronidazole	R
Oxacillin	R
Penicillin G / Penicillin V	R
Rifampicin	R
Vancomycin	R

Agents always considered inappropriate for treating gram-negative bacteraemia due to lack of appropriate concentration in the vascular compartment

Antibiotic	**Susceptibility imputation**
Oral nitrofurantoin	R
Oral fosfomycin	R
Oral trimethoprim	R
Oral pivmecillinam	R

In the following sections, the algorithms for each antibiotic-pathogen imputation are shown.

Citrobacter freundii (but not other Citrobacter species), Enterobacter spp., Serratia spp., Providencia spp., Morganella morganii, Hafnia alvei (these bacteria are typically constitutive AmpC producers)

Antibiotic	**Susceptibility Imputation**
Amikacin	If missing then .
Amoxicillin-clavulanate	R
Amoxicillin	R
Ampicillin	R
Ampicillin-Sulbactam	R
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S of cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	R
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then .
Cefuroxime	If missing then .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then . (though some species intrinsically R)
Doripenem	E meropenem
Ertapenem	If missing then.
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E impenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Notes

Nalidixic acid an acceptable alternative testing agent for ciprofloxacin but not other quinolones (this applies to all subsequent tables also)

E. coli, other Escherichia species, Shigella, Citrobacter species (apart from C. freundii), P. mirabilis

Antibiotic	**Susceptibility Imputation**
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then S if ampicillin-S; else .
Amoxicillin	E to ampicillin
Ampicillin	E to amoxicillin
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; if missing then S if ampicillin-S; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then .
Doripenem	E meropenem
Ertapenem	If missing then .
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E imipenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Notes:

Eschericia hermanii – this species is intrinsically R to pip-taz

Proteus mirabilis – this species is intrinsically R to tigecycline

Klebsiella species

Antibiotic	Susceptibility Imputation
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then .
Amoxicillin	R
Ampicillin / Amoxicillin	R
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then .
Doripenem	E meropenem
Ertapenem	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E imipenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Proteus vulgaris and Proteus penneri

Antibiotic	Susceptibility Imputation
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then .
Amoxicillin	R
Ampicillin	R
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	R
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	R
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	R
Doripenem	E meropenem
Ertapenem	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Gentamicin	If missing then .
Imipenem	If missing then .
Levofloxacin	If missing then .
Meropenem	If missing then S if imipenem-S; if missing then S if ceftriaxone-S or cefotaxime-S; else .
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; if missing then S if amoxicillin-S or ampicillin-S; else .
Tigecycline	R
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else R

Appendix 2 : Planned additional sub-group analyses

1. **ampC – 3rd generation cephalosporins.** For the ampC producing organisms, some professionals interpret these to be inherently resistant to all 3rd generation cephalosporins (3GC), regardless of in-vitro testing result. Our planned primary analysis is to interpret according to the in-vitro testing results. However, we will do an additional analysis of this sub-group of bacteria to see if defaulting all 3GC (ceftriaxone, cefotaxime, ceftazidime) to a resistant state changes the interpretation of the impact. We expect the number of these organisms treated with this type of antibiotic alone to be relatively small.

2. **ESBL – 3rd generation cephalosporins.** For organisms that are achieving 3GC resistance through expression of an Extended Spectrum β-lactamase (ESBL) enzyme, some professionals regard these bacteria as inherently resistant to all 3rd generation cephalosporins, regardless of in-vitro testing results. However, both EUCAST and CLSI both currently recommend reporting for ESBL-producing isolates based on the in-vitro test result for individual antibiotics. Therefore, according to current guidelines, it would be possible to have an ESBL-producing isolate that is ceftazidime-S and cefotaxime-R; or ceftazidime-R and cefotaxime-S. Our imputation rules therefore follow these guidelines, but we will make a planned additional analysis (once ESBL status is confirmed) to see a default interpretation of ESBL-producing organisms as being resistant to all 3GC changes the interpretation of impact. We expect the number of ESBL-producing organisms that have discrepant in vitro sensitivities between different 3GC antibiotics (eg ceftazidime-S and cefotaxime-R) to be relatively small.

3. **BLBI v carbapenem mortality impact.** Depending on numbers of suitable 3GC-resistant isolates available, we will make an additional analysis to investigate whether there is evidence of different mortality impacts of treating these with beta-lactam/beta-lactamase inhibitor combinations (eg piperacillin-tazobactam) versus carbapenem antibiotics (eg meropenem). This would represent a similar investigation to the MERINO trial, though using an observational format and the MBIRA study is not powered for this comparison.

4. **Inadequate dose**. If dose is considered to be “yes but inadequate” then primary analysis is to analyse this category of exposure separately. Secondary analysis is to consider this “yes but inadequate” as “inappropriate” antibiotic treatment (ie to merge this category with inappropriate antibiotic treatment). We expect there to be a relatively small number of antibiotic treatments in this “inadequate dosing” category.

Supporting references / further reading

1. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Magiorakos A et al, Clinical Microbiology and Infection, 2011
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4. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. Harris PNA et al, JAMA 2018 (=MERINO trial).
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