ALADDIN®

Antibiotic Levels And Daily Dose INdicator

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Aminoglycoside Levels And Daily Dose Mdicator

© John Turnidge and Jan Bell

Introduction

Aladdin is a computer program designed to adjust aminoglycoside doses based on the measurement of two aminoglycoside levels within a single dosing interval [1,2]. It is suitable for any form of dosing, either multiple or single-daily dosages. It is able to achieve this because it is not based on the traditional approach of 'toxic' peaks and troughs. Rather it adjust doses and/or dosing intervals based on achieving two target values of the 24-hour area-under-the-curve (AUC_{24}) and (optionally) the virtual peak (VP). These parameters have been chosen because they have been shown in human and animal studies to be the important pharmacodynamic parameters that predict the efficacy of aminoglycosides. Given two aminoglycoside levels taken several hours apart in a single dosing interval, it is possible to estimate AUC and VP based on mono-exponential (one compartment) pharmacokinetics. Thus this program requires two levels before it can make any estimations at all.

Basic computing requirements

Aladdin is a stand-alone Microsoft Office Access 2003 program that runs on a personal computer with Microsoft® Windows XP operating system.
As you use the Aladdin program, it accumulates data as would any database, allowing access to previous results on the same patient. The entered data and the calculated results are all stored in a separate database file (aladdata.mdb), so that if there are problems with the program they will not directly corrupt the database, and will remain current should the program itself be updated.

Loading Aladdin®

Copy your files

Before you do anything else, make a copy of the files and store in a safe place.

Installing on your hard disc

To install Aladdin you must:

1. Create a directory called C:\Aladdin
2. Download the Aladdin ZIP file from the website
3. Extract the files into the Aladdin folder
4. Store the program files in a safe place, one different from where you stored the copies.

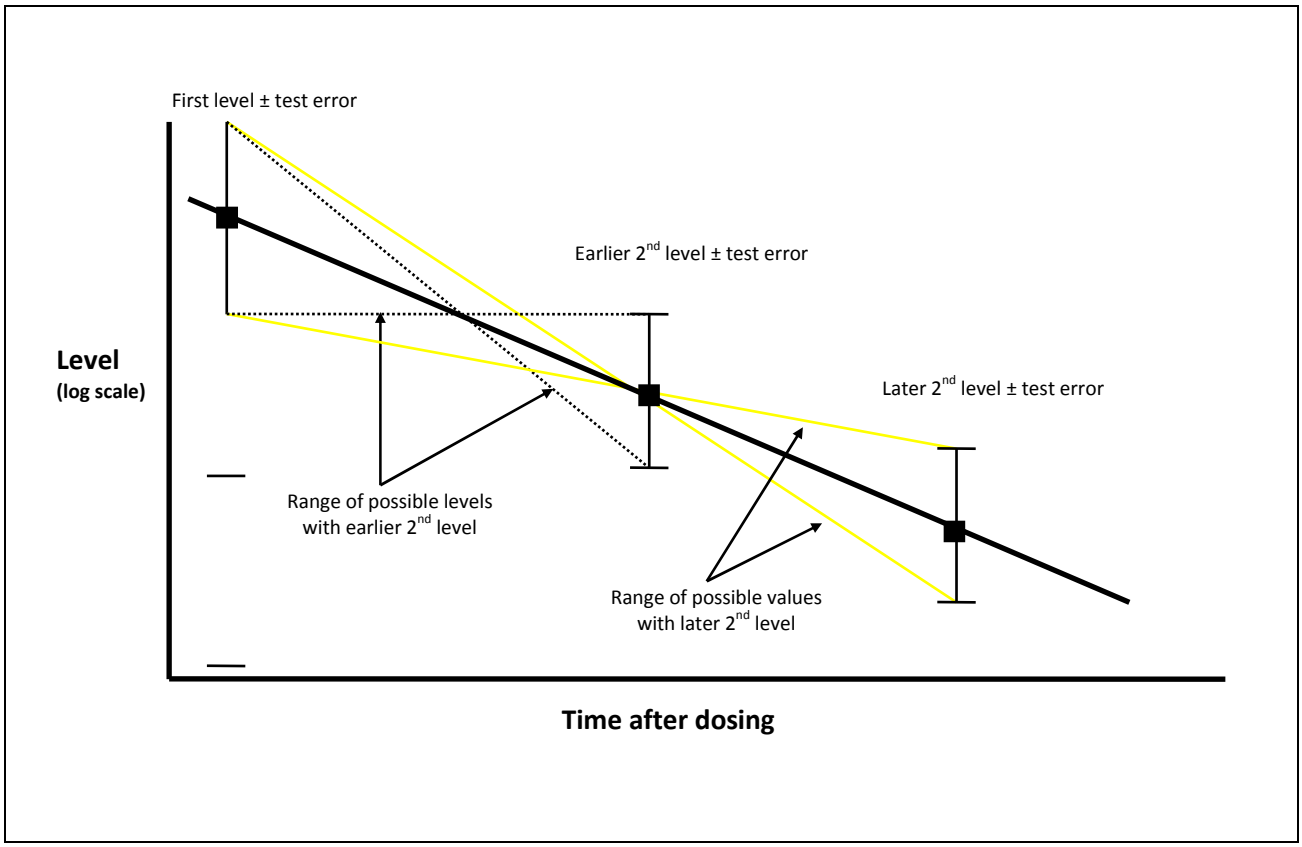
Starting Aladdin

You can start Aladdin by double-clicking the file called Aladdin.mdb.

Aminoglycoside Monitoring requirements

In order for Aladdin to perform any calculations, two levels are required to be performed. The first should be taken at the end of the infusion if giving by 15-30 minute infusion, or 15 minutes after a bolus dose. If an infusion runs too slowly, the first level should still be collected at the end of the infusion, and the time of first level entered exactly as it was, not what you hoped it would be. The program will cope with this just the same. The second level should be performed about 6 hours later. The timing of the second level is not critical. However, the second level must be measurable, that is, above the limit of detection of the assay. Most assays are or can be calibrated to detect levels at or above 0.5 mg/L. The second level must also either be taken within the current dosing interval, or be entered into the Data Entry screen as though it were in the same interval. The reason that we have selected 6 hours for the second level is that it is almost always measurable, even in patients with excellent renal function, and that results can usually be obtained from the assaying laboratory before the next dose is due. Later times, out to 10 hours or more, can be used (or 8 hours if using 8-hourly dosing), and will give more accurate estimates of the two key values, but run the risk of having an unmeasurable level in some patients. The reason that later times are more accurate relates to the error of testing, as demonstrated in Figure 1. When the time between the first and second level is short, the inherent error of the assay leads to a wider range of possible slopes of drug elimination than when the time between levels is longer. The timing of the second level that you chose for your institution will be determined by the dosage schedules that you normally recommend and the turnaround time for levels in your assaying laboratory. A short turnaround time will be an advantage because it allows

Figure 1



longer intervals between the first and second level while still guaranteeing that a result will be available in the ward before the next dose is administered. You will need to discuss this in detail with your assaying laboratory.

How Aladdin works

The screens

There are six screens.

Switchboard
Data Entry
Edit
View database
Print daily report
Database maintenance

The two screens that you will use most often are the **Switchboard**, which contains buttons for all the major functions of the program, and the Data Entry screen, where all the data entry and calculations are carried out.

Each screen also has a pull-down menu attached to the menu bar underneath the Title bar for each screen. These pull-down menus offer all the functions available on the screens themselves, and occasionally include other options for manipulating the screens.

Switchboard screen

There are six buttons on the switchboard that take you into all the functions of the program. They are:
Add New Patient Data takes you to the Data Entry screen, after you enter your initials.
Edit Patient Data takes you to the Data Edit screen.
View Database provides an on-screen view of all the patients entered on the database *{View Database}*
Print Daily Report prints a report of selected input and output values for all patients entered that day *{Daily Aminoglycoside Report}*
Database Maintenance allows you to archive all data and make backup copies of the input data. The archived data can be used for analysis totally separate from the program itself.
Exit exits the program completely.

Data Entry screen

This is reached via an intermediary screen requesting your initials (so that there is a record of who entered the data), and a button to click ("Data Entry Form") and an "exit icon". You will then be in the Data Entry Form proper. This Form is the standard method for data entry and results calculation. The screen has the following features:

- a pull-down menu in the menu bar at the top
- data entry fields in the top half of the form
- a "scroll" bar at the bottom that tells you how many records are in the database and that can take you to other records (if you happen to know the number of the entry)
- three buttons which are menu shortcuts for moving to a blank **New Record**, closing the screen (**Finish**), and generating a printout of the record (**Print**).
- an area at the bottom of the screen highlighting previously entered results from the same patient.

For data entry, some of the fields are compulsory while others are optional, as shown in the following table.

Table 1 Compulsory and Optional Data Entry Fields

Compulsory fields	Optional fields
Entered by	
Surname	First name
UR Number	Sex
Cystic Fibrosis	Date of birth
Drug	Height
Dose	Weight
Date and time of starting infusion	Serum Creatinine
Date and time of first level	
First level	
Date and time of second level	
Second level	

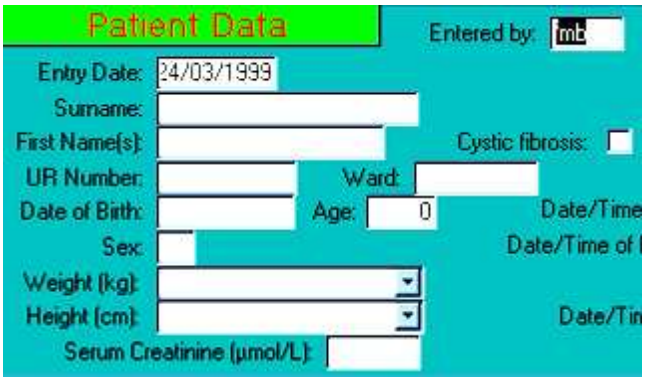
The {Entered by} field is automatically filled out, having taken the initials entered on the previous screen . Surname and UR number are compulsory data to avoid saving data without basic information about the patient that could be checked or searched for later, as well as to avoid duplicate entry. Drug, dose, dosing interval, dates, times and values of levels are compulsory because all subsequent calculations of pharmacokinetic parameters and dosage adjustments depend on them. Errors of entry are possible, although there is quite a lot of in-built error checking, such as the second level date and time being before the first level. If the results of calculations look bizarre, then more than likely there is a data entry error in the date, time or value fields for the levels.

All calculations on this screen are “live” and will generate a result as soon as they have found all the data they need. Although it should be obvious, the program cannot handle “>” or “<” values for the levels. An important point is that if the results don’t seem to be “quite right” for whatever reason, you should obviously check that the data have been entered correctly. Another common problem, not due to data entry, is an incorrect recording of the time of sample collection. It is tempting for those collecting the sample to round times up or down, or even put down the time that they should have taken it, rather than the true time (because they are embarrassed and forgot the collect it when it was scheduled!). It is essential that people who collect the samples are trained to put down the exact time of sample collection, and be reassured that there is no problem not collecting the sample exactly when scheduled. Also, if the time of collection are taken from a laboratory information system rather than the original request form, then there is a possibility that it has been entered incorrectly on the LIS.

Finally, Aladdin users should be clear that while it is essential to enter the infusion starting time, in general the duration of infusion will not affect the AUC calculation. This surprises many people, but rest assured the AUC remains the same regardless of the duration of infusion. Note, however, that because Aladdin uses the “virtual peak” to adjust once-daily (or less frequent) doses, dosing interval recommendations made by Aladdin will be affected if the infusion time is very long (>2 hours).

Patient Data (Figure 2)

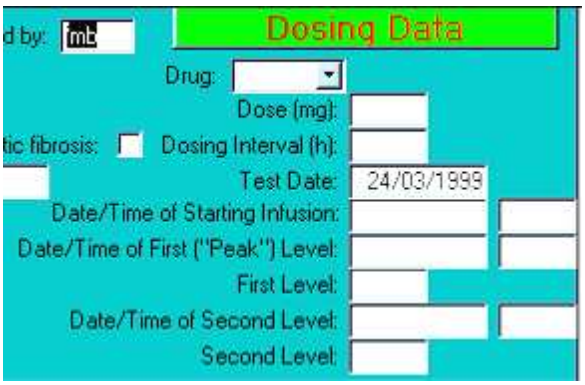
Figure 2



Entry date. This field that cannot be entered or altered. The date is taken automatically from the computer clock, so it is important to ensure that this is correct.
Surname. Surname can be entered in upper or lower case. It will automatically be converted to upper case on screen after you leave the field and go to the next.
First name. First name can be entered in upper or lower case. It will automatically be converted to upper case for the first letter and lower case for the rest after you leave the field and go to the next.
UR Number. This is the medical record number.
Cystic fibrosis. If the patient has cystic fibrosis, then check this box. The target AUC and virtual peak levels are adjusted accordingly.
Ward. Location of the patient
Date of Birth. You can enter the date in this field without adding the slashes between day and month, and month and year. However, you can put in the slashes if you are used to using them and the program will cope. This is the same for all of the date fields later on also. You must put the complete year in this date field, e.g. 1994, 1899.
Age. The patient's age is calculated automatically when you enter the patient's date of birth. The field itself cannot be entered.
Sex. Only M or F in either upper or lower case will be accepted.
Weight & Height. If you are able to obtain them, height, weight and creatinine are used in the calculation of creatinine clearance and mg/kg doses. It is common for people to know their height and weight on the old pre-metric scales. Pull-down lists are available for converting height in feet and inches to centimetres, and weight in stones and pounds to kilograms.
Serum Creatinine. This must be in millimoles per litre (mmol/L). Data entered as micromoles per litre will result in a wrong calculated value for estimated Creatinine Clearance. In neonates serum creatinine is not measured usually because the values can be quite misleading due to the fact that creatinine crosses the placenta. Therefore we have made it not possible to calculate creatinine clearance in neonates.

Dosing Data (Figure 3)

Figure 3



Drug. A pull-down list of aminoglycosides is also available in the drug entry field. The drug can also be selected by typing the first letter: g → GENtamicin, t → TOBramycin and a → AMIkacin. The first letter can be in either upper or lower case.
***Dose*.** This is entered in mg.
Dosing Interval. This is entered in hours.
Date/Time of Starting Infusion. You can enter the date in this field without adding the slashes between day and month, and month and year. You can put in the slashes if you are used to using them and the program will cope. If you do not use slashes you must put a 0 before single digit months. If you use slashes you do not need to do this. You must put in the complete year, e.g. 1999. If you do it will result in an error. Time is entered using the 24 hour clock. Minutes can be separated from hours by either a colon (:), or simply a period (.). The latter is quicker and easier; the period is automatically converted to a colon. Using a dash to separate minutes from hours brings up an error message.

***Date/Time of First ("Peak") Level*.** As for Date/Time of Starting Infusion. Note:

- The date of the first level must be the same or after the date of starting infusion
- The time of the first level must be after the time of the starting infusion.

First Level. Enter the result of the first level here in mg/L, which is the same as µg/mL.
Date/Time of Second Level. As for Date/Time of Starting Infusion. Note:

- The date of the second level must be the same or after the date of the first level
- The time of the second level must be after the time of the first level.

***Second Level*.** As for the First Level. Note:

- The second level must be lower than the first level.

When the second level has been entered the program immediately proceeds to calculate all the Pharmacokinetic Parameters and Dose Calculations. Results for the Patient Parameters are calculated earlier, as soon as all the information necessary to calculate them has become available.

Calculations

Patient parameters (Figure 4)

Adjusted body weight. The patient's height is used to estimate ideal body weight (not displayed) using an in-built formula that calculates it from ideal body mass index by age. This is then compared to the patient's actual weight. If the patient's actual weight is more than 25% above or below their ideal body weight then these 25% values are used for all calculations involving weight (creatinine clearances, doses in mg/kg). This

is a deliberate strategy to compensate for obesity and wasting which have been shown to give misleading predictions about aminoglycoside kinetics and dosing [3]. If weight but not height is available then the actual weight is used in calculations without compensating for abnormal body weight.

Figure 4

Calculated creatinine clearance. Creatinine clearance is calculated using the modified Cockcroft-Gault formula for adults [4] and with a modification of the method of Schwartz for adolescents and children [5]. Please note that if the creatinine clearance has actually been measured, it cannot be entered into the program.

Pharmacokinetic parameters (Figure 5)

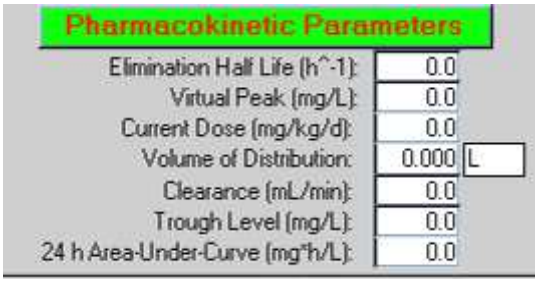
Aladdin calculates pharmacokinetic values from the dates/times and values of the levels, using weight/adjusted body weight when relevant. The calculations are based on a one-compartment, mono-exponential model of elimination, and the distribution phase is ignored. As aminoglycosides more closely follow a two-compartment model, this results in an underestimate of the AUC. However, the distribution phase of aminoglycosides is fairly rapid, and thus the underestimate is not great.

Elimination Half-Life. The elimination half-life is calculated in h.

Virtual peak. Because of the simplified model, virtual peak rather than true peak is calculated. This is the extrapolation of the kinetic curve back to time zero, the time of the bolus dose or the beginning of the infusion.

Current dose. For interest and comparison to new doses, the current dose is displayed in mg/kg if weight/ideal body weight is known.

Figure 5



Volume of distribution. As the one-compartment model has been used, there is only one possible volume of distribution calculable. It is displayed in L/kg if the weight/adjusted body weight is known, and in L if it is not.

Clearance. Drug clearance is included for comparison with creatinine clearance (CrCl) when the latter has been calculated. It is usually about two-thirds of the CrCl.

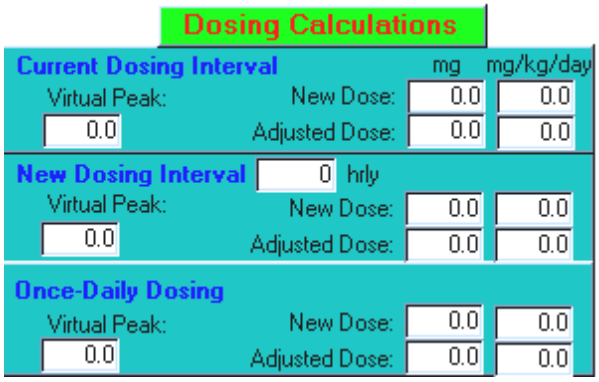
Trough Level. An estimated trough level in mg/L

24-hour Area-Under-the-Curve. The actual value calculated is the AUC over a 24 hour period (AUC_{24}). For multiple daily doses it is a simple multiple of the AUC calculated for dosing interval, and does not take into account the possibility of an increased AUC when doses are close together and/or trough levels are high. As

this occur infrequently, and as the AUC_{24} is likely to be well above target, this method of approximating AUC_{24} will rarely result in errors when calculating dose adjustments.

Dosing calculations (Figure 6)

Figure 6



All calculations for dosing are based around achieving a target AUC. In addition, a target peak level is taken into consideration. For calculations based on the current dosing interval and once-daily dosing a [**Low**] message pops up if this target peak level is not reached. For the new dosing interval calculation, this target peak level is used to drive the dose up and lengthen the dosing interval until the target peak level is reached or exceeded.

Target AUC values

Target AUC values have been selected for each of the three aminoglycosides available for intravenous use in Australia and are shown in Table 2 below. These values have been selected for two reasons. First, these are the approximate average values achieved with conventional dosing methods and doses normally chosen in Australia. In order to achieve target AUCs, initial doses do require adjustment according to age, with higher doses in children and lower doses for adolescents, younger and older adults. These doses are the ones we currently recommend for initial doses in patients with normal renal function, except in neonates, where doses require to the adjusted according to gestational age as well. These age-related doses for initiating therapy are shown in Table 3. The second reason for choosing the target AUC values comes from animal model data showing that close to maximum killing of *Enterobacteriaceae* requires an AUC of about 100 mg.h/L [6]. As satisfactory efficacy has been achieved with areas around 80mg.h/L for many years, and this area gives about 90% of maximum killing in an animal model, it is appropriate to stay with this slight lower target value. Higher values are used for cystic fibrosis patients because the target pathogen is almost always *Pseudomonas aeruginosa*, which has higher MIC values than enteric Gram-negative bacilli. Higher targets have also been suggested in one prospective study in nosocomial pneumonia [7]

Table 2 Target values for AUC and Virtual Peak used by Aladdin

	AUC (mg.h/L)		Virtual Peak (mg/L)	
Agent	Non CF	CF	Non-CF	CF
Gentamicin	80	100	> 12	> 15
Tobramycin	80	100	> 12	> 15
Amikacin	320	400	> 48	> 60

Target Virtual Peak Values

In vitro models have suggested that peak values at least 8-fold higher than the MIC appear to be important to prevent the emergence of resistance during [8]. Indeed in order to achieve this Nicolau et al. selected 7 mg/kg of gentamicin or tobramycin in order to reach peaks of 20 µg/L or more and thus be at least 8-fold higher than the median MICs of *Pseudomonas aeruginosa* (2 mg/L) [9]. While their experience appears to have been favourable in terms of efficacy and safety, these doses are much higher than appear to be necessary to achieve satisfactory efficacy in the majority of patients as seen in studies comparing once-daily to multiple daily doses [10]. We have selected 12 mg/L as a compromise (and 15 mg/L in cystic fibrosis). It is more than 8-fold higher than the modal MICs of susceptible *Enterobacteriaceae* but only 6-fold higher than the modal MICs of *P. aeruginosa*. It is also readily achievable with once-daily dosing using the conventional recommended doses. In addition, invasive pseudomonal sepsis should always be treated with combination antimicrobials, usually a ß-lactam in combination with an aminoglycoside. Thus reliance on a single agent and its peak to prevent the emergence of resistance is not so crucial issue. Nevertheless, one should consider higher aminoglycoside doses when treating serious pseudomonal sepsis.

Three sets of calculations are carried out, giving a choice for the prescriber/pharmacist of three methods of dosage.

Current Dosing Interval

All outputs are based on maintaining the current dosing interval. The **New Dose** is calculated exactly using the formula:

$$\text{New Dose} = \frac{\text{Old Dose x Target AUC}}{\text{24 Area-Under-the Curve}}$$

The **Adjusted Dose** is the New Dose adjusted to the nearest 10 mg (125mg for amikacin), unless the new dose is less than 80 mg (320mg for amikacin), in which case the Adjusted Dose is the same as the New Dose. The Virtual Peak that would be achieved by the New Dose is then calculated. If it is less than the Target Peak, a message box appears next to the level and the value itself is changed to red text.

New Dosing Interval

If the virtual peak achieved with dosage adjustment under the Current Dosing Interval is low, a New Dosing Interval is calculated based on an iterative algorithm. This increases the dosing interval, calculates the **New Dose** needed to maintain the target AUC and the **Virtual Peak** that it achieves until the target virtual peak is matched or exceeded. As before the **Adjusted Dose** is the New Dose adjusted according to the rules above.

Once-Daily Dosing

The **New Dose**, **Adjusted Dose** and **Virtual Peak** are calculated as above, but the dosing interval is set at once-daily.

Data Edit screen

The Data Edit screen looks almost identical to the Data Entry screen and has much the same features, including pull-down menu, a scroll bar and shortcut buttons. Data entry fields work the same as they do for Data Entry, except that they won't be blank to start with. You can click or tab into any field that you wish to edit or change. Calculated results will be updated automatically. The scroll bar at the bottom tells you how many records are in the database, the number of the current record (the screen opens with record 1), and

four buttons to navigate to the beginning of the database, the previous record, the next record and the end of the database in that order. If you click to button for the end of the database, and then the next record button, you will get a blank screen that can be used for a new patient entry.
The only significant differences between this screen and the Data Entry screen are that the New Record button is replaced with a **Find** button, which is a shortcut to finding the record that you wish to find. In order to do this you need to click or tab into the field that you wish to search first, such as Medical Record Number or Surname, and then click on the Find button. This comes up with a built-in Access® dialogue box which allows you to enter the information you are looking for and search with specific options as listed in the dialogue box. Once you have found the record you are looking for you need to manually close the dialogue box by clicking close. If you find the right patient but the wrong record, click on Find Next until you reach the desired record. You may then change or add to any of the data entry fields that you wish. In addition, you can choose to delete the record if you wish to by selecting this option off the Data Entry drop down menu in the top bar.

View Database screen

The View Database screen is an Access® Report function. It provides you with a direct look at the database for all fields and calculated results on individual patients. On a slower computer it takes some time for the program to load the data, especially if the database has become large. The information is spread over two pages in landscape format; thus, each two pages cover one part of the database. The screen pulls up normally in "zoomed-in" format. The cursor changes to a magnifying glass, and when clicked toggles between zoomed-in and zoomed out format. In zoomed-out format the information will be too small to read. This format is provided as a kind of "print preview", to check that the information will print correctly (see below).
Overall, this screen will not be needed very often. If you need to look up results on an individual patient then it is usually better to use the Find option on the Data Edit screen. However, there is a small disadvantage to finding results this way. Because of the way individual patient entries accumulate in the database (in entry order) it is not possible to see multiple entries from an individual patient sequentially in the Data Edit screen, let alone more than one set of results at a time. The View Database screen is, however, capable of this, because it sorts the database alphabetically before showing it on screen. Thus, all the results from a single patient appear in date order sequentially, no matter how far apart in the database the results are. You will usually have to "Page Down" to find these results. When this screen pulls up a second dialogue box is also pulled up, offering the option of printing the database in the format shown on screen. You can get an idea ahead of time about how it will look when printed out by zooming out on the view screen. The dialogue box also contains a switch for closing the View Database screen. Alternatively, this can be done from the menu as in other views.

Print Daily Report screen

The Print Daily Report screen is designed to offer the option of printing out a hard copy of selected results after they have been entered and calculated. It is assumed that this would only need to be done once daily. On choosing this option, a dialogue box appears with three buttons: **Print Preview**, **Print** and **Cancel.** The Print button prints the report directly, while the Print Preview button offers the option of viewing the printout on screen before it is printed. The Print Preview option pulls up a screen that has the same format as the View Database screen, that is, it is a report screen with a toggle for zoom. When the Print Preview is chosen, the dialogue box remains on top so that the Print and Cancel options are still available.
Only selected information is printed out in a daily report. This is deliberate, as it takes more than one page to include all the fields in the database, and it has been assumed that a more useful daily report should only print out on a single page. The following information is printed out in the daily report: Surname, UR Number, Test Date, Drug, Dose, Dosing Interval, First Level, Second Level, Current Interval - Adjusted Dose,

Current Interval - Projected Peak, New Interval - New Interval, New Interval - Adjusted Dose, New Interval - Projected Peak, Once-daily - Adjusted Dose, Once-daily - Projected Peak.

Database Maintenance

Clicking on this button brings up a dialogue box with three further buttons on it: **Backup Data, Archive Data**, and an **Exit** icon.

Backup Data. If the Backup Data button is selected, an output file of all the data that has been entered will be copied into a separate Access® database called aladbkup.mdb. Doing this daily is good practice, but at least weekly is advisable. The Backup routine stores a complete copy of the input data as a file called aladbkup.mdb.

Archive Data. The Archive Data button archives records over a selected date range to another location and then removes them from the main database. The data can be archived as a Table in an Access® database or an Excel® file, so that it can be used for analysis and studied in other ways, totally separate from the program itself. If archiving to an Excel spreadsheet, the Excel file must be renamed. When the database gets very large the speed of the program degrades to some extent, especially on slower machines. In these circumstances it will be necessary to archive the data.

Exit

Clicking on the exit button exits the program completely. On the pull-down menu there is an additional option to those available via the buttons. This is the **Close** option. This option can be ignored. It is designed for our (the developer's) control over the program design, and is of no use in the stand-alone program.

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Further Reading

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