MINISTRY of HEALTH & MEDICAL SERVICES

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DRUG USE EVALUATION REPORT

Investigating colistin usage in Fiji at the Colonial War Memorial Hospital, Lautoka Hospital and Labasa Hospital from August 2014 to November 2015

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The contents in the report do not necessarily reflect the views of Monash University.

Investigating colistin usage in Fiji at the Colonial War Memorial Hospital, Lautoka Hospital and Labasa Hospital from August 2014 to November 2015

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Introduction

Colistin is a 'last-resort' broad-spectrum antibacterial agent, that is used to treat multi-resistant *Acinetobacter baumannii* and certain other *spp.* Some Gram negative rods are intrinsically resistant to colistin i.e. *Burkholderia cepacia, Serratia marescens, Moraxella catarrhalis, Proteus* spp, *Providencia* spp and *Morganella morganii*.

Therefore, colistin use and misuse raises the potential for the development of significant bacterial resistance with profound clinical impact on the Fijian healthcare system. In addition, colistin is very expensive with the current procurement cost of colistin at AU$154.90 for a 150 mg vial. For these two reasons, colistin use at the three Divisional Hospitals: the Colonial War Memorial Hospital (CWMH), Lautoka and Labasa, must be strictly controlled. Recently, bacterial resistance to meropenem has emerged in the Divisional Hospitals and use of this last line antibiotic - colistin - has become necessary.

It should be an infrequently used antibiotic reserved for specific organisms only. Prescription of this antibiotic must be done in consultation with the Infectious Diseases Consultant Physician, and another relevant staff member until the AMS team is in place as well as the Pharmacy Department.

(Presentation: Colistimethate sodium expressed as 150 mg colistin base.)

There has been some concern that the use of colistin has not been in line with the recommendations that had been in place so a study of use was undertaken during November/December 2015 in the Colonial War Memorial Hospital (CWMH) in Suva and in the Divisional Hospitals in Labasa and Lautoka.

Aim of the study

The aim of the study was to determine the extent of the intravenous use of colistin and the rationale and reasons for its use during the time it has been available in Fiji.

1. Methods

In CWM, Lautoka and Labasa Hospitals:

1. Patient histories were sought for patients who had been treated with colistin and dispensing records from the Pharmacy PATIS (computer) system were retrieved.

   Microbiology reports from the Laboratory were consulted and the results added to the compiled information. Infectious disease records were also consulted.

   Restricted Antibiotic request forms were located and retrieved.

   Information relevant to colistin use was extracted from the above sources and combined records were analysed.
2. A study to gather information from physicians about their use of colistin was undertaken according to a set of questions (Annexe 1).
3. Microbiology and Infectious Diseases teams were interviewed concerning the use of colistin and the rationale for its use.
4. The Alfred Hospital in Melbourne was consulted concerning their recommendations for the use of colistin and a draft guidelines and protocol was prepared for Fiji.
5. The cost of colistin used in Fiji together with the cost of management of patients was calculated

6. Records of bacterial resistance during the previous five years were retrieved for reference.

The results of the above activities were analysed and a report prepared.

2. Results

2.1.Patients and Colistin Therapy

2.1.1 Retrieval of records

At the CWMH 19 patients were identified as having received colistin during the relevant period but only only six had full medical profiles and records reconciled. More complete information was assembled by combining information from pharmacy, microbiology and infectious disease records.

These records did not necessarily include the diagnosis.

Microbiology reports from the Laboratory were consulted and the results added to the compiled information. Infectious disease records were also consulted and relevant information was added to the compiled information.

Restricted Antibiotic request forms were located and retrieved.

A combination of the above records was used for analysis of colistin use.

2.1.2 Analysis of treatment records

2.1.2.1 CWMH

Patients and Colistin Therapy Information

- There were a total 19 patients in previous 18 months; of which only 6 could have full medical profiles and records reconciled. There were 18 adult (16 and above) and one paediatric patient
- All patients were within the intensive care setting, apart from one which was within the Acute Surgical Unit awaiting transfer to ICU.
- Fourteen patients who required colistin in previous 18 months had died. Four patients had died either before or the time immediate around first dose of colistin, a further two died within 48 hours of administration, a further seven died within the following fortnight. Of those deceased, five received only continuation therapy, and four had loading doses only. Three patients received loading doses and continuation therapy.
- There was inconsistency in frequency of dosing: Three patients were given single loading dose only, six were given 75-150 mg twice daily except for the paediatric patient given 15mg IV twice daily; nine patients were given the recommended loading and continuation therapy. Of those that survived, three received only loading doses; the other three had received only continuation therapy (daily or twice daily dosing for 1-2 weeks)
- Eight of the patients had been prescribed meropenem alongside colistin as synergistic therapy
- Nine had significant renal decline to end stage renal failure during the course of treatment. Of those deceased and who had renal function recorded (excluding 3) and the dose given prior to death (excluding one), six had significant renal decline, four had normal renal function. Of those that lived three had normal renal function, two had mild renal impairment. There was no apparent consideration of renal impairment in dose calculation despite recommendation for such.

Infection Characteristics

- *Acinetobacter baumannii was the* organism of infection in 15 cases, *Acinetobacter Junii* in two cases, followed by single infections by *Pseudomonas aeruginosa* and an unmarked MRO
- Organisms were identified from Blood Culture (5), Pleural Aspirate, Tracheal Aspirate (3), Peritoneal Fluid, Sputum, IDC tips (2), Wound Drain Swabs were taken from wounds, pus and burn wounds, central lines, endotracheal tube and cerebro-spinal fluid.

2.1.2.2 Lautoka Hospital

1. A total of six patients were found sensitive to colistin during the 12 months of 2015 (January to December). Histories were not available for all patients so Information was extracted from patient files that were found and from the Pharmacy software – PATIS – and from microbiology records to give as comprehensive picture of colistin use as possible. The pharmacy records did not necessarily include the diagnosis.
    - Two were identified *Pseudomonas Aeroginosa* (CSF & Blood culture) and the remaining four were *Acinetobacter Baumanii* (Blood culture, NGT tip x 2 and IDC tip)
    - Two patients out of the six received colistin twice daily for seven days therapy and survived with one patient receiving synergistic combination therapy with meropenem Injection 500mg three times a day.
    - The remaining four patients died before administration of colistin injection.
    - One of the patients who did not survive was also sensitive to ceftazidine. While waiting for the availability of colistin injection, the patient started with ceftazidine for three days and then died.

2.1.2.3 Labasa Hospital

1. There was only one relevant patient and the necessary complete information was extracted from the patient file together with the Pharmacy PATIS records.
    - Mid 2015, only one patient required the use of colistin but due to the unavailability of colistin at Labasa, the patient was transferred to CWM and died. Colistin testing strips are not available at Labasa Hospital and there was no further laboratory request done for Colistin sensitivity test for this patient .

2.2 Physician Study results

2.2.1 CWMH, Lautoka and Labasa

Eight practising physicians at CWMH, 10 physicians at Lautoka and 10 physicians at Labasa were interviewed regarding colistin and its use within the hospital. Full responses are listed in Annexe 2

Responses covered the following issues that were general across the three hospitals:

1. The need for colistin is determined by an infection control problem, with all aspects of Infection prevention and control (IPC) negligible and products for management of IPC out of stock. 'Lack of budget' is given as the excuse for inadequate supplies and systems.
2. First line antibiotics are usually not in stock.
3. Better data acquisition and analysis of sensitivity / resistance profiles are needed. Recorded sufficiently, but of no use if it cannot be used for future planning and tracking.
4. Antimicrobial Stewardship is non existent, and the need for AMS is urgent.
5. Not all prescribers are aware of the policy for access to colistin.
6. Given the level of nosocomial infection, and the high fatality rate, there is need to introduce colistin earlier, if there is resistant infection almost certain need to initiate colistin therapy immediately

7. Several aspects of the implementation of the policy resulted in delayed treatment: 48 hours delay in microbiology turnaround for results, and longer with frequent shortage of reagents and equipment in the laboratory and unavailability of consultants for signatures.
8. Surgical departments have the largest apparent misuse of antimicrobials and require greater pharmaceutical supervision.
9. Equivalency between colistimethate sodium and base; Units and Milligrams a constant source of confusion and guidelines are unavailable to staff despite requests. Sanford and Frank Shann are primary sources for Antimicrobial Therapy.
10. STGs are not readily available and are out-of-date and better references are needed.
11. There is poor communication between pharmacy and other departments and Antimicrobial Week was poorly done. Many clinicians were unaware, and those that were aware were disappointed in the complete lack of activities, promotions and education.

2.3. Interviews with Microbiology and Infectious Diseases departments

2.3.1 Infection Characteristics

Acinetobacter baumannii was the organism of infection in 15 cases, *Acinetobacter junii* in two cases, followed by single infections by *Pseudomonas aeruginosa* and an unmarked multi-resistant organism. Organisms were identified from Blood Culture (5), Pleural Aspirate, Tracheal Aspirate (3), Peritoneal Fluid, Sputum, IDC tips (2), Wound Drain Swabs were taken from wounds, pus and burn wounds, central lines, endotracheal tube and cerebro-spinal fluid.

Outbreaks were recorded in 2014, 2015

2.3.2 Microbiology

Points made across the three hospitals were similar:

Training is needed and supply of necessary laboratory reagents and equipment are not reliable.
The work load is high for the number of staff, resulting in slow turnaround of results.

2.3.3 Infection Prevention and Control (IPC)

Points made across the three hospitals were similar:

1. IPC is completely inadequate and almost non-existent
2. There is some monitoring, with little intervention
3. Limited training and education and training
4. No budget or allowance, monetary or time given for IPC
5. No guidelines or protocols are written, up to professional knowledge
6. All actions are responsive with very little preventative actions
7. Supply of all basic antimicrobial supplies: soaps / disinfectants, gowns, cleaning and other equipment is not organised

2.4. Protocol for use of colistin

The current protocol was considered impractical in terms of the steps required to access colistin-resulting in serious delay in treatment, inadequate in terms of guidance, and in urgent need of review.

As a result of consultation with the Alfred Hospital and consideration of the results of this study, a guideline for the use of colistin in Fiji was prepared for recommendation to the NMTC.

The guideline recommends

1. **During a confirmed outbreak** of an organism resistant to all other available (or appropriate)

antibiotics, colistin may be prescribed as empirical therapy for patients with clinical evidence of severe infection, for a maximum of 72 hours pending results of microbiology specimens.

Appropriate microbiological specimens **must** be obtained PRIOR to the commencement of administration of colistin and sent to the Lab for testing.

If the culture proves positive continue treatment according to the directions below.

If infection with a multi-resistant organism is not microbiologically confirmed after 72 hours, colistin must be ceased and appropriate alternative antimicrobial therapy instituted. Once the outbreak is declared to be controlled by the Infection Control Unit, empirical antibiotic therapy must revert to a non-colistin containing regimen.

2. **In the non-outbreak setting,** colistin may only be prescribed to a patient where there is clear clinical evidence of significant infection AND a microbiological specimen is confirmed positive for an organism resistant to all other available (or appropriate) antibiotics.
3. For use of colistin in all circumstances, the colistin 'Restricted antimicrobial request form' **must** be completed and signed by 2 consultants, including a member of the AMS team. After hours when signatures are not available, telephone verbal authorisation is acceptable with signature the next day.

The complete guideline including dosage recommendations and conditions for use is Annexe 3

2.5. Costs of colistin use and management of patients

- Colistin was bought from Alphamed Australia for AU$154.90 per vial

  Initially 100 vials were purchased – 27/8/2014 - and it became available at FPBSC almost a month later. All was dispensed in CWMH. A second consignment of 20 vials was purchased 31/3/2015.

  The total cost of the colistin was AU$18,588.00
- NICU outbreak at CWM cost $32,000 FD
- Airlift per patient from Labasa to Suva for treatment cost $17,000.00 FD

2.6. Records of *Acinetobactor Baumanii* resistance

Resistance (%)	2013 Q3 N=77	2014 Q1 N=72	2014 Q2 N=14	2014 Q3 N=13	2014 Q4 N=45	2015 Q1 N=45	2015 Q2 N=79
Cephazolin	66.2	73.6	57.1	76.9	84.4	84.4	70.9
Ceftrioxone	83.1	80.6	64.3	92.3	86.7	88.9	69.6
Gentamicin	93.5	77.8	78.6	69.2	91.1	84.4	78.5
Nitrofurantoin	24.7	13.9	28.6	30.8	20.0	20.0	25.3
Nalidixic Aucd	11.7	12.5	7.1	30.8	17.8	15.6	11.4
Cefaclor	23.4	5.6	28.6	23.1	20.0	15.6	25.3
Sulfamethoxazole	74.0	66.7	71.4	53.8	86.7	60.0	55.7
Chloramphenicol	92.2	77.8	71.4	92.3	95.6	97.8	89.9
Ciprofloxacin	85.7	55.6	14.3	53.8	91.1	75.6	55.7
Meropenem	80.5	55.6	42.9	61.5	93.3	77.8	67.1
Ampicillin	100.0	95.8	100.0	100.0	100.0	100.0	100.0
Septrin	0.0	27.8	7.1	0.0	6.7	2.2	1.3
Amikacin	81.8	31.9	71.2	53.8	77.8	68.9	58.2
Cephatholin	22.1	1.4	0.0	0.0	0.0	0.0	2.5
Trimethoprim	20.8	13.9	28.6	7.7	17.8	22.2	27.8
Piperacillin & Tazobactam	1.3	1.4	0.0	7.7	0.0	0.0	0.0

Table 1.0 Resistance profiles of *A. Baumanii* isolates recorded at CWMH between July 2013 and June 2015 (Records unavailable after this period at time of collection). Due to data indifferences 2013 Q4 has been excluded.

Sensitivity (%)	2013 Q3 N=77	2014 Q1 N=72	2014 Q2 N=14	2014 Q3 N=13	2014 Q4 N=45	2015 Q1 N=45	2015 Q2 N=79
Ceftriaxone	2.6	4.2	29.8	0.0	0.0	2.2	12.7
Gentamicin	10.4	8.3	59.5	15.4	4.4	11.1	12.7
Sulfamethoxazole	9.1	5.6	39.7	23.1	2.2	13.3	12.7
Ciprofloxacin	18.2	15.3	14.3	23.1	26.7	22.2	35.4
Trimethoprim	0.0	1.4	9.9	0.0	0.0	0.0	1.3
Amikacin	18.2	43.1	50	30.8	26.7	26.7	32.9
Meropenem	16.9	16.7	7.1	23.1	11.1	20.0	32.9
Chloramphenicol	5.2	5.6	39.7	7.7	4.4	0.0	2.5
Cefazolin	1.3	1.4	9.9	0.0	0.0	2.2	2.5
Nalidixic Acid	2.6	5.6	39.7	0.0	2.2	2.2	17.7
Ampicillin	0.0	4.2	29.8	0.0	0.0	0.0	0.0
Cotrimoxazole	0.0	1.4	9.9	7.7	0.0	0.0	0.0
Colistin	9.1	0.0	0.0	0.0	2.2	6.7	6.3
Vancomycin	0.0	0.0	0.0	0.0	0.0	2.2	0.0
Nitrofurantoin	1.3	0.0	0.0	0.0	0.0	0.0	1.3

Table 2.0 Sensitivity profiles of *A. Baumanii i*solates recorded at CWMH between July 2013 and June 2015 (Records unavailable after this period at time of collection). Due to data indifferences 2013 Q4 has been excluded.

Ward	Number of *A.Baumanii* Isolates
Adult ICU	78
NSW	20
ASW	9
ENT/Burns/Plastic	4
NICU/PICU	9
Children's Ward	3
AMW/CCU	5
MMW/WMW/Sukuna	8
ED/SOPD/NDC	10
Lancaster/MICU	3
PW/Beqa	2
Korovou/Navua/Wainibokasi/TB Ward	5

Table 3.0 : The number of A.baumanii isolates recorded per ward at CWMH between June 2014 and April 2015. Credit Colonial War Memorial Hospital Microbiology Department 2015.

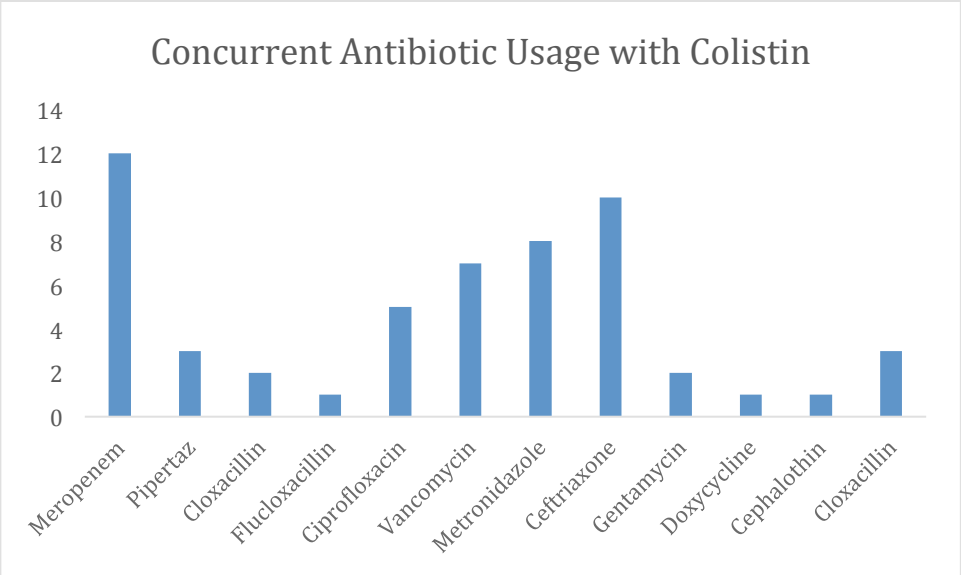

Table 4 : Antibiotics prescribed in the four weeks prior to and during Colistin treatment at CHMW.

Outbreaks in the period 2014 to 2015
Lautoka - No outbreaks
Labasa – No outbreaks
CWMH
2014 : Three outbreaks in NICU – (All *Klebsiella pneumonia* producing extended spectrum beta-lactamase (KPN-ESBL))
2015 :One outbreak ICU (*A.Baumanii* penicillin resistant) and NICU 2 (Both KPN ESBL)

3. Discussion

3. 1 Retrieval of records of patients' treatment

Comprehensive patient histories are not maintained and complete patient histories are crucial:

- **Drug use evaluation studies (DUEs):**

  DUEs cannot be undertaken appropriately in the absence of patient histories including diagnoses and treatment. DUEs will be flawed if they rely on dispensing records, or other records. Studies aimed at assessing prescribing of particular medicines for particular diagnoses will not be possible in the absence of patient records.

- **Stock of medicines:**

  Patient treatment records must be the basis of quantification of ongoing needs and the quantities of medicines needed in stock. A reliable supply of the right first line medicines means prescribers would not have to prescribe alternative medicines by default. In addition, patient records are the basis of quantification for developing disease/condition statistics in Fiji; and the numbers of diseases/conditions also can determine the quantities of medicines that must be procured for treating those disease/conditions.

3.1.1 Patients and Colistin Therapy Information

- The high fatality rate suggests that where the use of colistin is warranted, it should be available and administered promptly. The protocols for accessing colistin need to take this situation into account.
- All patients were in intensive care settings so their management should have been optimal. However, the existence of renal failure in nine of the CWMH patients together with the inconsistency of dosing that was discovered indicate that very clear guidelines are needed for the use of colistin.

Antimicrobial Stewardship should be established in the hospitals as a priority in order to:

- Undertake systemic evaluation of treatment of infections
- Monitor and track antibiotic prescribing and resistance patterns
- Develop regular reporting mechanisms on antibiotic use and resistance - to doctors, nurses and relevant staff
- Educate clinicians about resistance and optimal prescribing

3.2 Physician Study results

3.2.1 infection control

Responses relating to reasons for the prevalence of MDR infections focussed of the absence of appropriate infection prevention and control (IPC). Physicians emphasised the continual reliance of 'lack of budget' as the excuse for inadequate IPC supplies and systems but they found that assertion unconvincing.

There is no excuse for lack of stock. Systems must be put in place where orders for stock are based on actual assessment of need for optimal IPC and good stock management must be a priority. The FPBSC Warehouse staff must be consulted to develop a system for assessment of needs and the prompt supply of adequate stock. Stock-outs must not be tolerated.

All patients were in intensive care settings so their management should have been optimal. IPC in ICUs must be meticulous to avoid further nosocomial infection of patients.

In recognition of the crisis in IPC the CWM staff and the Australian Volunteer program have recruited a specialist IPC training coordinator to assist the IPC staff for one year in the three hospitals, to develop an efficient, effective and sustainable IPC program. The assignment description in Annexe 5. It is hoped that the assignment will begin in June or July 2016.

3.2.2 Guidelines for prescribing and protocols for the supply of colistin

Whilst some identified the application for restricted antimicrobials as laborious and unnecessarily complex, the majority believe the application was sufficient and just in its use. Several aspects of fulfilling the criteria of the current policy resulted in delayed treatment: 48 hours delay in microbiology turnaround for results, and longer with frequent shortage of reagents and equipment in the laboratory and unavailability of consultants for signatures. Speed and accuracy of the assessment of the resistance profile of the causative agent is vital for initiating prompt treatment to achieve a positive outcome for the patient.[1]

In some cases colistin was prescribed by default because first line antibiotics were out of stock. There was also some dissatisfaction with pharmacy services.

Because of colistin's position as 'last line' in the therapy of MDR organisms and its cost, a special form for access for this drug that includes detailed guidance for its use is needed, bearing in mind the constraints associated with the time needed for microbiology results and the need for authoritative signatures. A draft protocol and access form has been prepared after collaboration with the Alfred Hospital in Melbourne (Annexe 3). As well as addressing the issues identified here it is necessary to ensure that the form is readily accessible and all staff are aware of it and know how to use it.

The existence of Standard Treatment Guidelines (STGs) for antibiotics was not universally known and the books had not been well distributed. Attempts to comply with the STGs were often frustrated by stock-outs of first line antibiotics.

The EML 4 articulates the STGs that provide guidance for the use of the listed medicines. Restricted medicines are marked clearly, together with the identification of the guidelines to use for prescribing those medicines. Therefore, if restricted medicines are used according the STGs as they should be, that process will cover the use of Restricted Antibiotics according to the correct procedures. The active presence of an Antimicrobial Stewardship team in the hospital would facilitate the monitoring of antibiotic prescribing practices and could encourage compliance with the STGs.

All the above issues need to be addressed and can be addressed with straight forward measures.

Initially all prescribers and other staff need to be aware of the STGs and their role. The third edition of the Antibiotic Guidelines was published in 2011[2] almost five years ago. It is time for that to be revised.[3] Revision of the Fiji Antibiotic Guidelines could provide the opportunity to involve prescribers and increase their ownership of the STGs.

Antimicrobial Stewardship must be put in place in all 3 hospitals to monitor all aspects of infection control and antimicrobial use.

3.2.3 Reliable supply of stock and STGs.

Responses from physicians highlighted the unreliability of supplies of medicines and of laboratory and IPC supplies. The maintenance of patient records of conditions and treatment is crucial. These records enable calculation of supplies to order based on need as well as providing the necessary records as described earlier in this report. A culture of good record keeping must be developed. First line antibiotics must be in stock. In the absence of the correct medicines, irrational prescribing of medications will occur.

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[1] Belkum A et al. 2014. Meropenem/colisitn synergy testing for multidrug-resistant *Acinetobacter Baumannii* strains by a two dimensional gradient technique applicable in routine microbiology. *J Antimicrob Chemother* doi:10.1093/jac/dku342
http://jac.oxfordjournals.org/content/early/2014/09/19/jac.dku342.full.pdf

[2] Antibiotic Guidelines, 3rd Edition 2011, available from http://www.health.gov.fj/?page_id=198

[3] Review of the Antibiotic Guidelines 3rd edition is supported by the interval between revisions of the Australian Antibiotic Therapeutic Guidelines: 1978, 1979, 1982, 1984, 1987, 1990, 1992, 1994, 1996, 1998, 2000, 2003, 2006, 2010, 2014. In the earlier years the interval was only 2 years then more often 3 years. In the last 10 years there have been three editions with an interval of 4 years between editions.

Similarly records of activities must be kept together with documentation of the necessary supplies needed for both the laboratory and for IPC. It is the responsibility of the FPBSC warehouse to supply the needs as calculated according to need. There is no excuse for continuing stock-outs of medicines and supplies.

All current STGs should be in the possession of every single prescriber as well as other staff. The Fiji Essential Medicines List 4 (EML 4) should also be available for every prescriber. If there are insufficient they should be ordered from FPBSC.

3.3. Microbiology and Infectious Diseases

3.3.1 Infection Characteristics

With the presence of *Acinetobacter baumannii* and other multidrug-resistant (MDR) pathogens in Fiji, it is crucial that the Fiji National Antibiotic Resistance Action Plan 2015 is implemented and Antimicrobial Stewardship should be established in the hospitals as a priority.

Adherence with Antibiotic STGs is crucial. For that to take place there must always be first line antibiotics available.

3.3.2 Infection prevention and control

Infection Prevention and Control (IPC)

Responses from microbiology staff regarding IPC highlighted in detail the inadequacies of the system. The problems must be addressed and as explained in 3.2.1, In recognition of the crisis in IPC the CWM staff and the Australian Volunteer program have recruited a specialist IPC training coordinator to assist the IPC staff for one year in the three hospitals, to develop an efficient, effective and sustainable IPC program. It is hoped that the assignment will begin in June or July 2016.

Given the ability of *A baumannii* to adhere to surfaces, form biofilms, display antimicrobial resistance and acquire genetic material from other unrelated species,[4] it is crucial that very well designed procedures are put in place to deal with the organism; and strict infection prevention and control procedures are followed meticulously.

3.4 Development of a protocol for the use of colistin.

The information gathered during this study indicates that the use of colistin according to the protocol that has been circulated is very patchy. Further it has been shown that following the procedures dictated by the protocol form causes delays in administration of effective therapy and many patients have died.

The shortage of the supplies necessary for the laboratory to undertake its tasks also has a negative impact on the delivery of prompt accurate results.

At the same time it is clear that the lack of effective infection prevention and control has led to the prevalence and outbreaks of multi-drug resistant nosocomial infections that require specialised antimicrobial therapy.

It is clear that the situations regarding laboratory procedures and infection prevention and control must be addressed and ameliorated. However, while patients are suffering from MDR organisms such as *A Baumannii* they must be treated promptly and effectively.

Given colistin's position as 'last line' in the therapy of MDR organisms, the complications around its administration and its cost, a special form for access for this drug that includes detailed guidance for its use is needed, bearing in mind the constraints associated with the time needed for microbiology results and the need for authoritative signatures. Therefore as well as consulting senior infectious diseases

[4] Aoife Howard, † Michael O'Donoghue, † Audrey Feeney, and Roy D. Sleator. 2012. *Acinetobacter baumannii* An emerging opportunistic pathogen. Virulence. 2012 May 1; 3(3): 243–250 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3442836/ accessed April 15, 2016

physicians and Consultants who have worked in Fiji, the Alfred Hospital in Melbourne was consulted for advice concerning the management of MDR organisms.

A Guidelines and protocol for the use of colistin was developed for the current Fiji setting. An Antimicrobial Stewardship team is needed urgently in the hospitals to facilitate the use of colistin according to correct procedures.

3.5 Costs of colistin and patient management

Colistin was bought from Alphamed Australia for AU$154.90 per vial with the total cost of the colistin purchased to date AU$18,588.00.

Colistin is widely available as a generic product from experienced wholesalers outside Australia,

- CIPLA in India has a reputation for manufacturing pharmaceutical products of good quality. However, it is recognised that all products imported to Fiji must satisfy the Fiji regulatory requirements associated with GMP and quality control; of both manufacturer and product.
- A number of different companies products were investigated in the exploration of the availability of colistin at a more affordable price.
- Products from a range of Indian companies were around the same price.

As a benchmark, the CIPLA product called Xylistin is shown here

(US$1 = 66.55 Indian Rupees

Xylistin 1 MIU (power as colistin methate sodium) 10 ml vial 715 Indian rupees = US$ 10.74

Xylistin 2 MIU (power as colistin methate sodium) 10 ml vial 12755 Indian rupees = US$ 19.15

It is suggested that it would be sensible to explore the option of procuring CIPLA colistin rather than the Australian product.

The incurred cost of outbreaks and the cost per patient airlifted to Suva highlight the need for meticulous infection prevention and control as well as the need for prompt treatment with appropriate antibiotics in the Divisions as well as in Suva. A reliable supply of infection control and laboratory reagents and equipment must always be available together with reliable supplies of necessary medicines must always be present in the Divisions as well as in Suva. Such measures would be much more cost-effective than bearing the cost of outbreaks and transfers of patients.

3.6 Resistance patterns and records

In relation to Tables 1 and 2, with the exception of essentially complete ampicillin resistance, there is quite an extensive range seen in the variation of resistance profiles on a quarterly basis. Of great concern is the upper ranges of resistance to meropenem, peaking at over 90% which would indicate the need for colistin as essential in such cases of subsequent infection. Whilst the variations in resistances to aminoglycosides are quite broad, there should be some clinical consideration of the use of gentamicin in instances of such infection, given the limited options available and the apparent sensitivity.

Of particular interest is the negligible resistance to piperacillin and tazobactam.

However the clinical relevance of such MCS must be questioned given that many of the antibacterial agents, inclusive of equivalences are not readily and continually available at CWMH and further some are no longer used in clinical practise. It would be recommended that the agents used in such MCS be revised such that they be reflective of current clinical therapies.

Further, whilst instances of complete resistance were noted (19 cases in 2013 Q3), further isolates whilst resistant to apparently all had not been strictly identified as completely resistant (as not known if all agents had been tested).

The range of variations in both sensitivity and resistance exemplify the importance of adherence to correct antimicrobial practises. As such it would be suggested that clinicians have a wider range of agents made available for use in such therapies, such that the most appropriate and effective therapies can be

utilised, resulting in better patient outcomes in addition to limiting the development of antibacterial resistance.

In relation to Table 4, given colistin to be the 'last line' antibiotic for treatment of Gram negative resistant bacteria, it would be expected that its usage would be subsequent to previous meropenem therapy, given expected susceptibility of most anaerobes and Gram negative bacteria inclusive of *Acinetobacter Spp*. to such therapy. However it was found that often meropenem was prescribed concurrent with colistin. Initially this may seem to be contradictory to antimicrobial principles and guidelines for Colistin usage in excessive antibiotic usage, how such regimes are used in instances of limited susceptibilities. Whilst complete resistances may be indicated, instances of some susceptibility may exist and concurrently resistances may occur where indicated as sensitive. Such instances left untreated may confer resistance and spread resistance to such therapies. As such using meropenem even though indicated as resistant, could have an antimicrobial effect on any organisms that are possibly colistin resistant and still contain some meropenem sensitivity, even though indicated otherwise. This is one regime which limits the spread of resistances to and extends the clinical life of such last line antimicrobial therapies. Further recent literature has indicated a synergistic relationship between the concurrent use of carbapenems and colistin in increasing antimicrobial activity, a relationship which is yet to be fully understood. However this has been one of the very few developments in the use of such highly restricted therapies, and would be key in extending the clinical life of colistin.[5]

[5] Belkum A et al. 2014. Meropenem/colisitn synergy testing for multidrug-resistant *Acinetobacter Baumannii* strains by a two dimensional gradient technique applicable in routine microbiology. *J Antimicrob Chemother* doi:10.1093/jac/dku342
http://jac.oxfordjournals.org/content/early/2014/09/19/jac.dku342.full.pdf

4. Conclusions

4. 1 Retrieval of records of patients' treatment

Comprehensive patient records are not routinely maintained and retrievable so drug use evaluation studies (DUEs) cannot be undertaken, diagnoses statistics cannot be maintained and uantities of medicines needed for treating those disease/conditions cannot be estimated.

4.1.1 **Patients and Colistin Therapy Information**

- Patients treated with colistin were suffering from infections that warranted the treatment with colistin.
- Patient doses were not consistent and there was incomplete understanding of dosage requirements.
- A detailed guideline for the use of colisitin is needed.

4.2 Physician Study results

4.2.1 infection control

Physicians consider suboptimal infection prevention and control to be the cause of nosocomial infections and they attribute this situation largely to lack of stock of appropriate supplies and equipment.

4.2.2 Guidelines for antibiotic use and protocols for the supply of colistin

- Not all physicians were familiar with the existing procedures. The procedure needs to be revised. Its specifications need to be clear and practical and it needs to include clear guidelines for dosing
- Delay in microbiology turnaround for results, in line with the requirements of the current access form, and longer with frequent shortage of reagents and equipment in the laboratory as well as unavailability of consultants for signatures resulted in delayed administration of colistin and in many cases unsuccessful treatment.
- The Standard Treatment Guidelines (STGs) are not widely available and there is inadequate awareness of the role and value of these guidelines. There is insufficient ownership of the STGs.
- Attempts to comply with the STGs by physicians who valued them, were often frustrated by stock-outs of first line antibiotics, and restricted antibiotics were prescribed.
- The third edition of the Antibiotic Guidelines was published in 2011[6] almost five years ago. It is time for that to be revised.
- Antimicrobial Stewardship must be put in place in all three hospitals to monitor all aspects of infection control and antimicrobial use according to STGs and protocols .

4.2.4 Reliable supply of stock and STGs.

A reliable supply of stock of all medicines is not maintained. Patient records are not maintained routinely.

STGs were not widely in the possession of the physicians and the value of the books was not appreciated as well as it should be.

Adherence to STGs means that treatment will be predictable. Maintenance of patient records of conditions and treatment according to STGs and protocols is crucial as a basis of quantification of needs of medical supplies to order.

It is important that physicians own the concept of STGs and that every edition is distributed widely so that every prescriber has copies of all titles.

[6] Antibiotic Guidelines, 3rd Edition 2011, available from http://www.health.gov.fj/?page_id=198

The EML 4 should also be available for every prescriber. It articulates the STGs that provide guidance for the use of the listed medicines. Restricted medicines are marked clearly, together with the identification of the guidelines to use for prescribing those medicines.

If first line restricted medicines are always in stock and used according the STGs, that process will cover the use of Restricted Antibiotics according to the correct procedures.

The active presence of an Antimicrobial Stewardship team in the hospital would facilitate the monitoring of antibiotic prescribing practices and could encourage compliance with the STGs.

4.3. Microbiology and Infectious Diseases

4.3.1 Infection Characteristics

A baumannii is an important opportunistic organism found in Fiji that is responsible for serious nosocomial infections.

Strict infection prevention and control procedures are not in place to avoid nosocomnial infections

The is no Antimicrobial Stewardship in place to Undertake systemic evaluation of treatment of infections

- Monitor and track antibiotic prescribing and resistance patterns
- Develop regular reporting mechanisms on antibiotic use and resistance - to doctors, nurses and relevant staff
- Educate clinicians about resistance and optimal prescribing

Records of activities are incomplete as is documentation of the necessary supplies to order for both the laboratory and for IPC.

The FPBSC has not taken responsibility for maintaining distribution of appropriate quantities of suitable supplies for the laboratory to undertake tasks efficiently and promptly.

4.3.2 Infection prevention and control

Infection Prevention and Control (IPC)

Appropriate infection prevention and control (IPC) are lacking throughout the hospital.

Appropriate products for IPC are not in stock

Lack of effective IPC is a primary cause of nosocomial infectious disease.

There is no excuse for lack of stock. Systems must be put in place where orders for stock are based on actual assessment of need for optimal IPC and good stock management must be a priority. The FPBSC Warehouse staff must be consulted to develop a system for assessment of needs and the prompt supply of adequate stock. Stock-outs must not be tolerated.

There was unanimous expression that Fiji is facing an antimicrobial crisis and that all aspects of Infection control are negligible and proper hygiene should be the target, along with patient education. It was recognised that AMS is non-existent and the need is urgent.

In recognition of the crisis in IPC the CWM staff and the Australian Volunteer program have recruited a specialist IPC training coordinator to assist the IPC staff for one year in the three hospitals, to develop an efficient, effective and sustainable IPC program. It is hoped that the assignment will begin in June or July 2016.

4.4 Development of a protocol for the use of colistin.

- Use of colistin according to the existing protocol is very patchy.
- Following the procedures dictated by the current protocol have caused serious delays in administration of effective therapy and many patients have died.
- A revised guideline and protocol is needed as a priority

- It was sensible to consult the Alfred Hospital in Melbourne concerning their approach to the management of MDR organisms.
- An Antimicrobial Stewardship team is needed urgently in the hospitals to facilitate the use of colistin according to correct procedures.

4.5 Cost of colistin and patient management

- The cost of colistin bought from Alphamed Australia is excessive (AU$154.90 per vial with the total cost of the colistin purchased to date AU$18,588.00).
- Purchase of a quality assured generic product would be much more cost effective for example Xylistin from Cipla at less that 10% of the cost from Australia.
- Effective IPC would reduce the incidence of nosocomial infections and the subsequent cost of treatment.
- Reliable supplies of laboratory reagents and medicines in the Divisional Hospitals would enable prompt treatment of affected patients on site and avoid the cost of transport to Suva.

4.6 Resistance patterns and records

The need for colistin may have arisen from the failure of other agents. *Acinetobacter Spp.* are typically susceptible to antibiotics such as ciprofloxacin and gentamycin, which could identify the need for their moderate use prior to Colistin prescription.

Implementation of the National AMR Plan 2015 is also essential as it will also address the issue of irrational prescribing of antibiotics in the private sector. There is no control over ciprofloxacin prescribing and dispensing by private physicians and pharmacists

5. Recommendations

The following recommendations should all be implemented as priority.

5. 1 Maintenance of records of patients' treatment

- Comprehensive patient records must be routinely maintained and retrievable so drug use evaluation studies (DUEs) can be undertaken, diagnoses statistics can be maintained and quantities of medicines needed for treating those disease/conditions can be estimated.
- The records should document procedures followed when needed for the use of Restricted Antimicrobials such as colistin and meropenem
- A printed of electronic format for the complete documentation of patient information should be designed and put in place

5.2 Physician Study results

The following recommendations address the areas identified by physicians as needing attention during the interviews.

5.2.1 infection control

- Effective infection prevention and control (IPC) procedures should be put in place immediately
- Relevant supplies for the above activities must be in stock.
- A system must be initiated to facilitate the maintenance of records of stock needed and used and for quantifying needs and submitting orders to FPBSC regularly
- FPBSC must supply the necessary stock for IPC promptly

5.2.2 Guidelines for antibiotic use and protocols for the supply of colistin

- A revised comprehensive and practical guideline for the management and treatment of MDR organisms with colistin and for access to colistin must be in place and used. (A draft document is Annexe 3)
- Awareness to be created of the policy so that prescribers are well versed with requirements
- All Standard Treatment Guidelines (STGs) must be supplied to all prescribers
- Essential Medicines List (EML) 4 must be supplied to all prescribers so they can see which STGs specify the source of guidance for the use of each medicine.
- Prescribers should adhere to the protocols in the Antibiotic STGs when prescribing antibiotics.
- Antibiotic Guidelines should be revised because it is almost 5 years old and should be up-to-date.
- In the process of revision of the Antibiotic Guidelines feed-back and comments should be sought from prescribers and considered by the writing committee to enhance ownership by prescribers
- A form should be prepared and circulated electronically to prescribers to collect their comments and feedback.
- Antimicrobial Stewardship and training must be put in place in all three hospitals to monitor all aspects of infection control and antimicrobial use according to STGs and protocols .

5.2.3 Reliable supply of stock and STGs.

- Patient records of treatment according to guidelines and protocols must be maintained routinely as a basis for calculating needs of medical supplies to order.
- A suitable appropriate order form in line with the supplies needed should be designed to facilitate ordering.

- A clinical pharmacist should work with the wards to ensure full understanding of the system of maintaining stock and to ensure that orders accurately reflect needs.
- FPBSC must supply the stock needed in the quantities needed.
- Sufficient stock in Lautoka and Labasa would avoid the need to airlift patients to Suva at a cost of $17,000.
- A clinical pharmacist should check that copies of STGs and EMLs are possessed by physicians ensure that orders for these books are made to FPBSC when they are needed.
- Physicians should make note of any feedback or comments on the recommendations delivery to the National Medicines and Therapeutic Committee (NMTC).
- The Antimicrobial Stewardship team must be active in the hospital to facilitate the maintenance of the correct level of antibiotic stock, monitor antibiotic prescribing practices and to encourage compliance with the STGs.

5.3. Microbiology and Infectious Diseases

5.3.1 Infection Characteristics and infection control

5.3.1.1 Laboratory – see also 5.6

- Develop an assignment description for a laboratory specialist supported under the Australian Volunteer scheme to help strengthen the laboratory over a period of one year. (In collaboration with CWM staff an assignment has been submitted and accepted for recruiting. The assignment description is Annexe 4)
- Antimicrobial Stewardship must be in place to undertake systemic evaluation of laboratory activities and infection control and to educate clinicians about resistance and optimal prescribing

5.3.1.2 Infection prevention and control

- Strict infection prevention and control procedures must be in place to avoid nosocomial infections
- Review of Infection Prevention and Control Manual is essential (It is outdated by approximately10 years)
- There must be an active role of the IPC unit in outbreaks with provision of updates to stakeholders
- Complete documentation of all microbiology activities must be maintained.
- An assignment must be developed to recruit assistance from a specialist supported the Australian Volunteer program to work with the IPC team for one year to strengthen all procedures and develop a competent and sustainable program. (The assignment was developed in collaboration with the CWMH staff and accepted and recruitment is underway. The assignment description is Annexe 5.)
- Put systems in place for orders for stock to be based on actual assessment of need for optimal IPC and good stock management as a priority. Stock-outs must not be tolerated.
- The FPBSC must take responsibility for maintaining distribution of appropriate quantities of suitable supplies for the laboratory to undertake tasks efficiently and promptly.

5.4 Development of a protocol for the use of colistin.

- Consider the revised guideline and protocol (Annexe 3) and adjust as needed then put it into use promptly.
- Install the Antimicrobial Stewardship team urgently in the hospitals to facilitate the use of colistin according to correct procedures.
- Develop awareness of the policy promptly
- Develop awareness of the existence of the AMS team as soon as it is in place.

5.5 Cost of colistin and management of patients

- Procure Colistin more cost-effectively than from Alphamed Australia at AU$154.90 per vial with the total cost of the colistin purchased to date AU$18,588.00.
- MRA should call for dossiers from Indian companies listed in Annexe 6 and evaluate their specifications for GMP and quality control. For example CIPLA who provide Colisitin as follows at less than 10% of the cost fro Australia.
    - Xylistin 1 MIU (power as colistin methate sodium) 10 ml vial 715 Indian rupees = US$ 10.74
    - Xylistin 2 MIU (power as colistin methate sodium) 10 ml vial 12755 Indian rupees = US$ 19.15
- Purchase colistin more cost-effectively.

5.6 Resistance patterns and records

1. Microbiology should present antimicrobial susceptibility information to relevant stakeholders
2. Proper quantification of lab reagents and sensitivity discs must be undertaken (review of current quantities) with merging resistant and sensitivity patterns.
3. FPBSC must ensure continuous availability of essential reagents.
4. FPBSC should employ Laboratory Personnel who looked after the procurement of laboratory consumables and reagents. An officer familiar with laboratory activities will be in a good position to advise on products and procure for the laboratory.
5. Proper record keeping should be adhered to all time. Essential data to be readily made available to relevant authorities.
6. Laboratory results should be provided to pharmacy so relevant records can be included in PATIS.
7. Susceptibility results must be available within 48-72 hours.
8. The laboratory must work in close collaboration with IPC.
9. There must be active involvement in the recommended Antimicrobial Stewardship team
10. Create awareness on choice, nature, collecting, handling and testing of specimens for detection of infection