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CASE REPORT

Polymyxin B induced generalized skin hyperpigmentation in infants

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Abstract:

Polymyxin B is a polypeptide antibiotic derived from Bacillus polymyxa. It has bactericidal activity against aerobic gram negative bacteria including multidrug resistant Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae and carbapenemase producing Escherichia coli. One of the common adverse reactions noted among infants receiving IV Polymyxin B was increased in skin pigmentation. In our literature search, there has been no report on Polymyxin B induced skin hyperpigmentation. We are reporting this additional adverse reaction noticed as the use of Polymyxin B is becoming prevalent.This is a prospective case study on the infants who have been treated with IV Polymyxin B due to multidrug resistant bacteria in Neonatal Intensive Care Unit (NICU), Sarawak General Hospital (SGH) from 2nd February 2012 till 31th July 2012. The skin tone changes were captured with a digital camera with same shooting mode from day 0 to at least day 14 of IV Polymyxin B and continued to be monitored until discharges. Data collection is done by studying on the skin tone from the photos captured of the recruited patients. All the 16 infants, their skin tone were progressively darkened throughout the treatment period. 8 infants recruited have their skin tone reverted to baseline colour averagely at 46 days post IV Polymyxin B treatment and 3 infants have their colour became fairer averagely at 34 days post IV Polymyxin B treatment. Remaining 5 infants had persistent hyperpigmentation upon discharged or deceased. Among the 5 infants who had persistent skin hyperpigmented, 1 of them died due to uncontrolled septicaemia 14 days after treatment completed and the remaining 4 had their skin fairer during subsequent clinic follow up.Reversible generalised cutaneous hyperpigmentation is a common complication noted in premature infants receiving polymyxin B. The mechanism of skin hyperpigmentation secondary to IV Polymyxin B is still unknown. Larger sample size is needed to prove the adverse reaction more evidently.

Keywords: *Polymyxin B, hyperpigmentation, infant*

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Introduction

Polymyxin B is a polypeptide antibiotic derived from Bacillus polymyxa. It had become commercially available in 1959. It has bactericidal activity against aerobic gram negative bacteria including multidrug resistant Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella pneumoniae and carbapenemase producing Escherichia coli [1].

There was an outbreak of Acinetobacter baumannii infection in Neonatal Intensive Care Unit (NICU), Sarawak General Hospital (SGH) in early of the Year 2012 and this organism is only sensitive to Polymyxin B, thus IV Polymyxin B was given to Acinetobacter baumannii septicemia patients.

Pediatric dosage of IV Polymyxin B for the

treatment of septicaemia is 15,000-40,000 units/kg/day in two divided doses [2]. It associates with significant adverse effects. Documented well known adverse effects are nephrotoxicity, neurotoxicity, urticaria rash and thrombophlebitis at intraveneous injection sites [3]. Hence it uses is limited to only when other safer modern antimicrobial agents are ineffective or contraindicated. The emergence of multidrug resistant organisms globally has lead to increase usage of Polymyxin B. One of the striking adverse drug reactions noted observed among all infants receiving IV Polymyxin B during the study period was increased in skin pigmentation. In our literature search, there has been no report on Polymyxin B induced skin hyperpigmentation. Herein we are reporting this undocumented adverse effect that has been noticed in infants who received IV Polymyxin B.

Skin hyperpigmentation is the darkening of skin due to the increasing production of melanin in the body [4]. It can be due to various reasons, for example, inflammation, exposed to stimuli such as sunlight or it associates with diseases [4]. However, mechanism of skin hyperpigmentation induced by IV Polymyxin B is still unknown.

Material and Methods

Study design

This is a prospective observational case study. All eligible infants were included after written informed consent of their parents.

Inclusion criteria

All infants, regardless of gestation ages and races, who have admitted to Neonatal Intensive Care Unit (NICU), Sarawak General Hospital (SGH), and have been treated with complete course of IV Polymyxin B due to multidrug resistant septicaemia, were eligible for participation in the study.

Methods

Study was carried out from 2nd February 2012 till 31th July 2012, total of six months. Photo shooting of the infants was conducted in whom their skin tones were captured with a digital camera with same shooting mode during the treatment period. The complete treatment duration is 14 days with dosage of 15000 units/ kg 12 hourly.

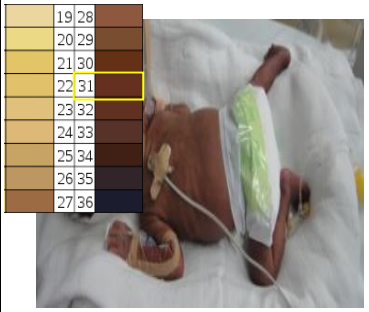
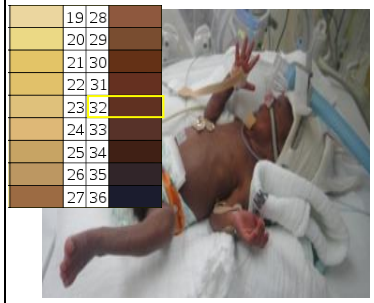
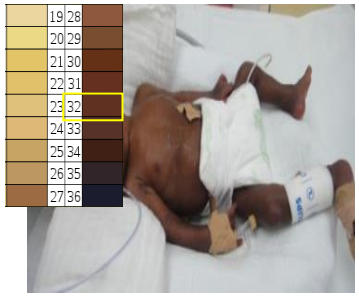
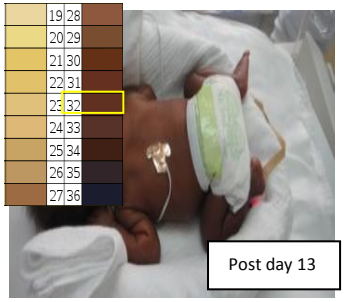
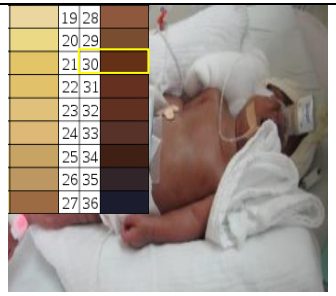
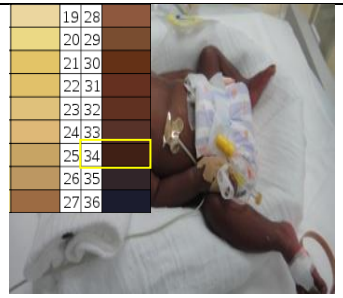
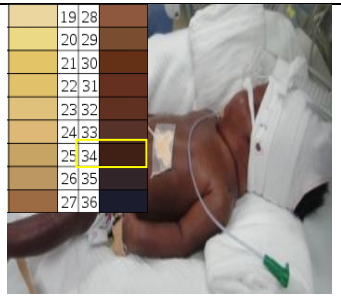
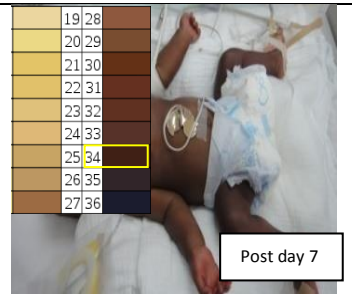
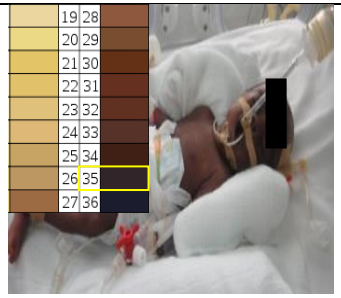
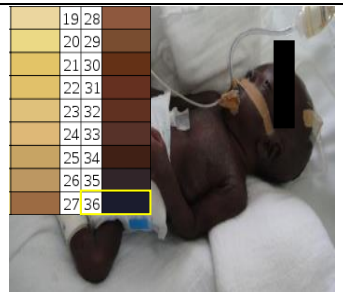
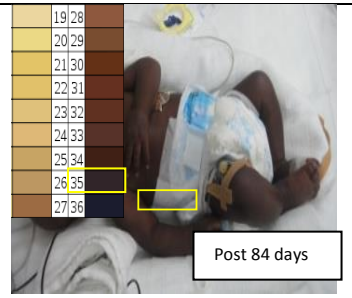
Subjects were recruited from NICU, SGH and chosen based on the inclusion criteria. Treatment duration must be at least 14 days and subjects must remain treated in the ward without transferring out or discharging home. Data collection is done by studying on the skin tone from the photo captured of the recruited patients from day 0 until the day when patient either transferred out from NICU, discharged home or deceased. The skin tone difference is visually classified by using Felix von Luschan Skin Color Chart, as shown in *Appendix A*. Felix von Luschan Skin Color Chart is used to classify human skin color, which contains of 36 different scales.

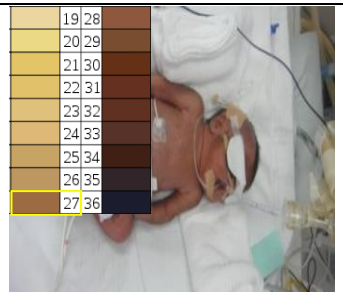
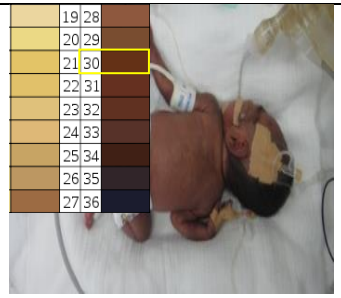
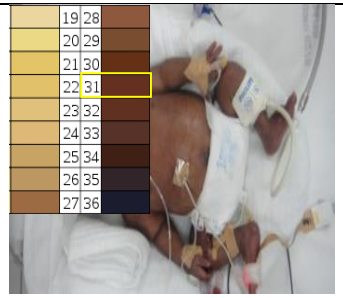
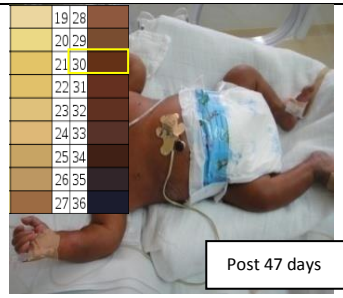
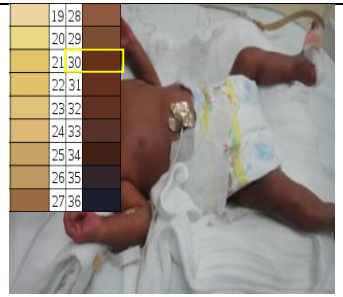
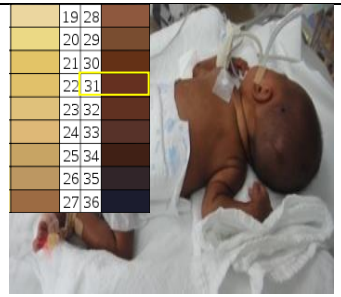
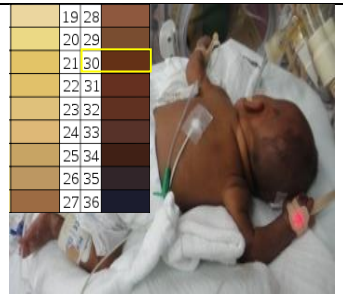
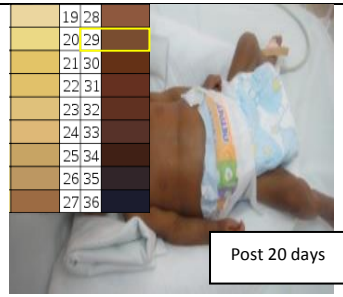
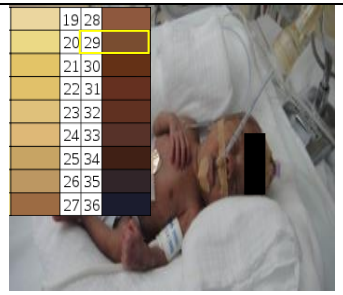
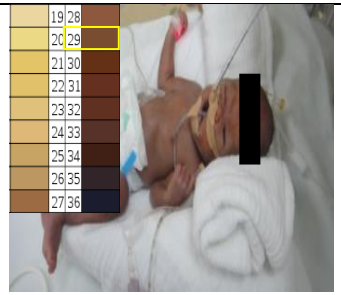
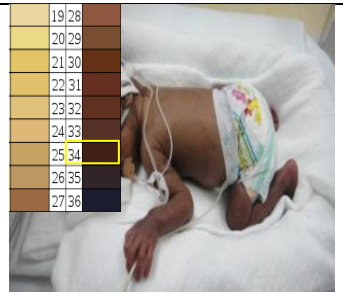
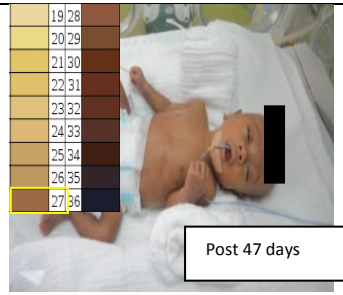
A designed form which consists of patient demographics, ward medications, concomitant antibiotics and culture and sensitivity test, for data collection, is shown in *Appendix B*. Concomitant antibiotics will be assessed to rule out other causes that can increase in skin pigmentation.

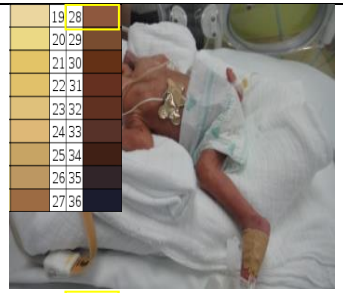
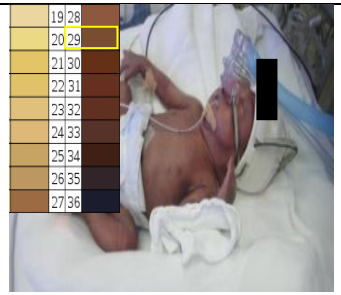
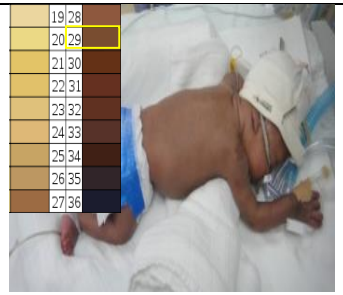
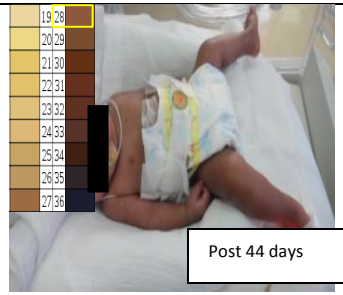
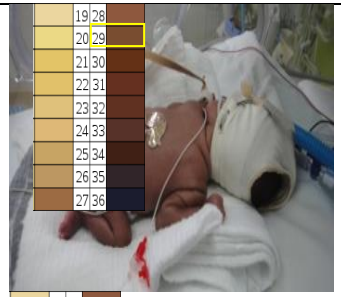
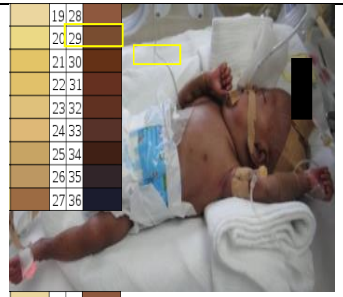
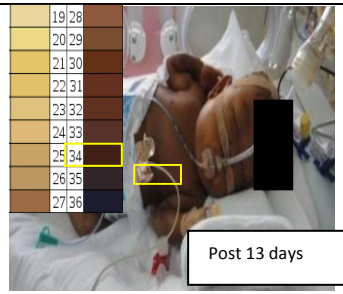
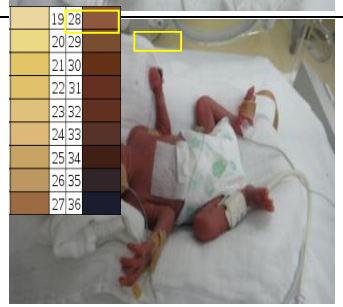
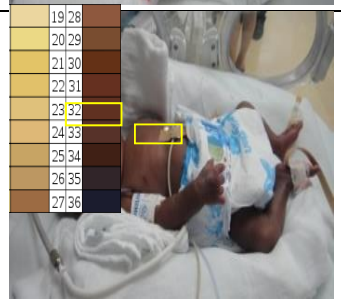
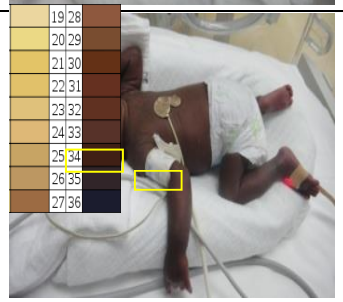
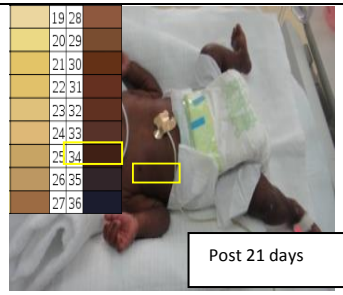
Results

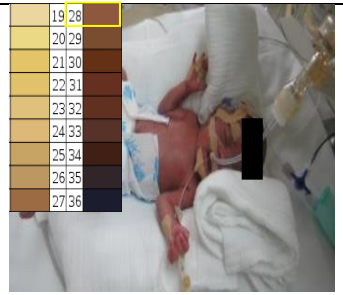
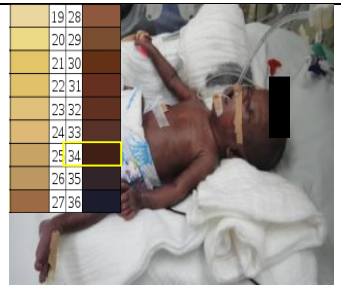
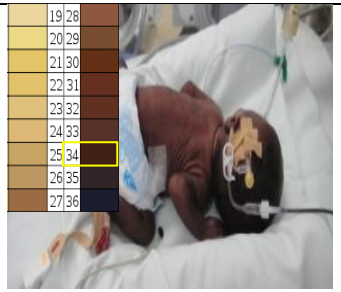
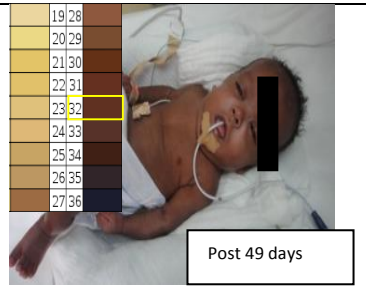
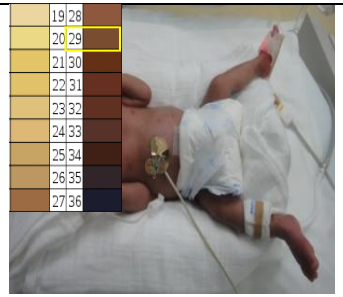
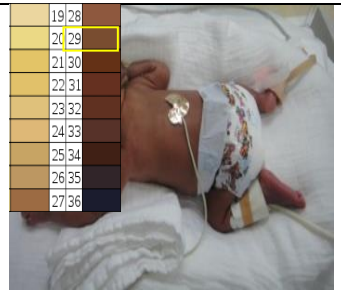
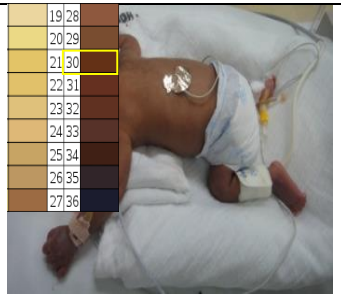
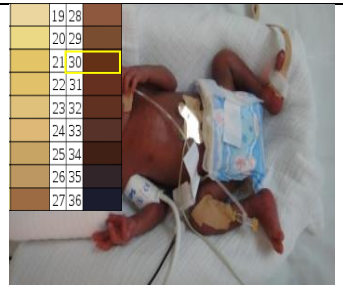
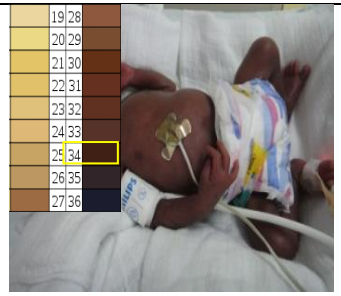
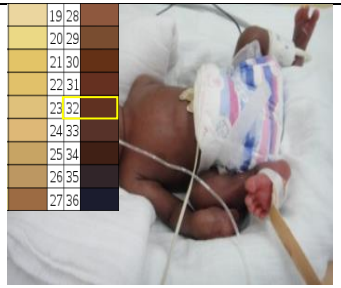
Between February 2012 and July 2012, a total of 16 infants were eligible to be recruited in the study, where Iban contributed 44%, 31% were Malay, 19% were Chinese and 6% were Indian. All the infants were born premature with gestational ages from 25-31 weeks with mean gestation age of 27 weeks. The mean age of starting treatment was 30 weeks with gestational ages ranging from 27-35 weeks. All the 16 infants, their skin tone were progressively darkened throughout the treatment period. 8 infants recruited have their skin tone reverted to baseline colour averagely at 46 days post IV Polymyxin B treatment and 3 infants have their colour became fairer averagely at 34 days post IV Polymyxin B treatment. Remaining 5 infants had persistent hyperpigmentation upon discharged or deceased. Among the 5 infants who had persistent skin hyperpigmented, 1 of

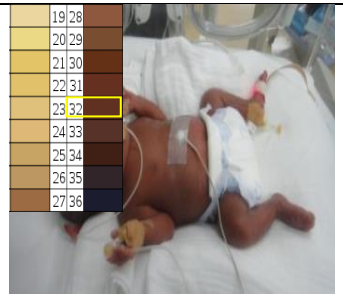
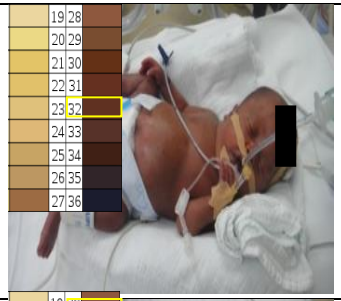
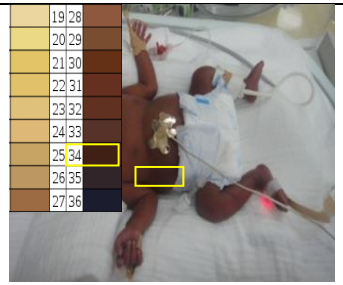
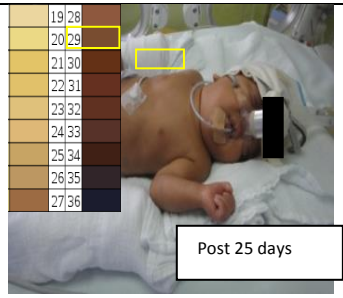
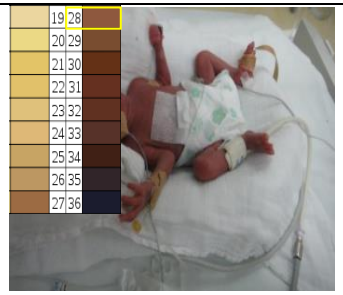
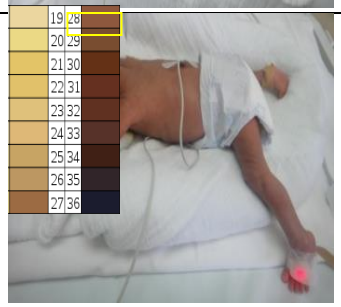
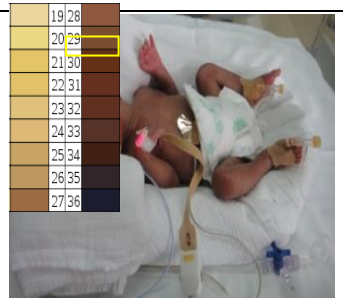
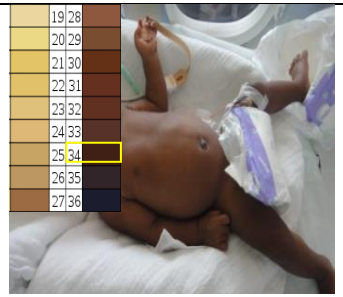
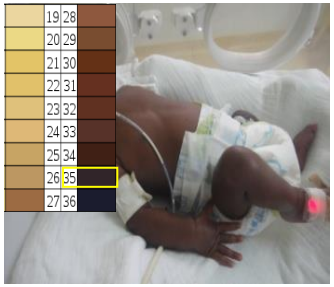
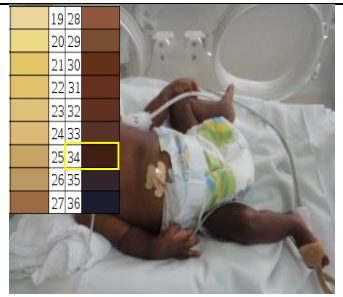
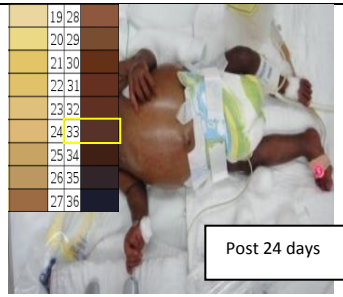
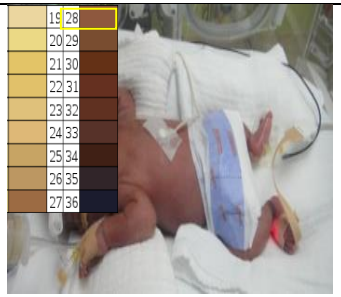
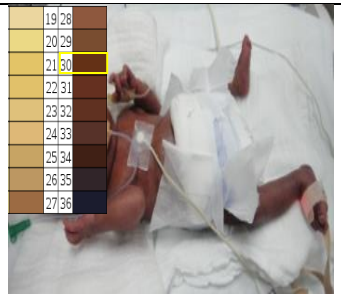
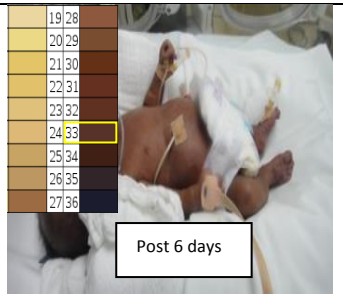
Table I. Photos of infants recruited with their progression of skin tone changes (Note: Yellow box in the picture indicates the scale of skin tone which has visually classified)

Number of subject	Baseline skin tone (Day 1 of IV Polymyxin B treatment)	Day 7 of IV Polymyxin B treatment	Day 14 of IV Polymyxin B treatment	Skin tone post IV Polymyxin B treatment
1				
2				
3				

4				 Post 47 days
5				 Post 20 days
6				 Post 47 days

7				 Post 44 days
8				 Post 13 days
9				 Post 21 days

10				 Post 49 days
11				 Post 21 days
12				 Post 99 days

13				 Post 25 days
14				Photo not available as patient has transferred out from NICU
15				 Post 24 days
16				 Post 6 days

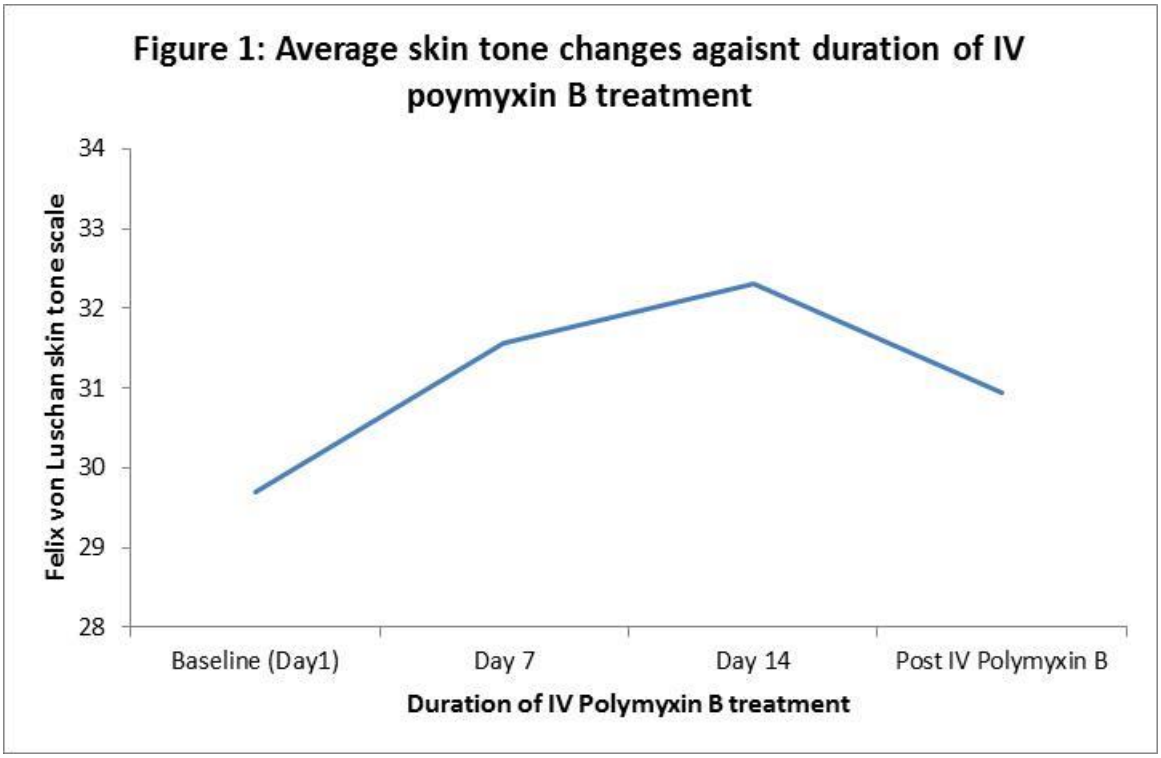


Figure 1. Average skin tone changes (by using Felix von Luschan skin tone scale) among all infants recruited against duration of IV Polymyxin B treatment

them died due to uncontrolled septicaemia 14 days after treatment completed and the remaining 4 had their skin fairer during subsequent clinic follow up.

The photo of infants recruited with their progression of skin tone changes are presented in Table 1.

As shown in Figure 1, average skin tone changes throughout the treatment period were classified and plotted. Averagely, skin is progressively darken from scale 30 to scale 32 throughout the treatment period and regressed to scale 31 post IV Polymyxin B treatment.

Discussion

Melanogenesis produces melanin. Melanin is the determinant of skin tone, and it comprises of eumelanin, which contributes to black and brown colour, and pheomelanin, which contributes to pink to red colour [5].

Polymyxin B is documented with slower clearance in neonates and in infants as the drug level found to be higher as compared to adults, with cumulative effect. This effect is likely to be exaggerated among premature babies. The etiology of hyperpigmentation due to Polymyxin B is unknown; however, proposed mechanism would be due to the release of histamine by Polymyxin B. Polymyxin B releases histamine [6]. Melanogenesis can be induced by inflammatory mediators, such as histamine [6]. Histamine metabolized and derives imidazoles, which is a 5 membered ring with molecular formula of C3H4N2. Itis found to stimulate the melanocytes (melanin producing cell, which found in stratum basale of skin epidermis), thus eumelanogenesis [7,8]. Besides, histamine also promotes tyrosinase activity, which is an enzyme that controlling the production of melanin [9]. Another possible factor that would be attributed to skin hyperpigmentation is the duration of treatment as the skin tone became darker in the end of treatment.

A report in year 2007, also reported that skin hyperpigmentation has been observed in adult patients receiving combination therapy of IV Tigecycline and IV Polymyxin B [10]. However, pigmentation abnormalities are denied to be associated with Polymyxin B and it is believed that hyperpigmentation is associated with Tigecycline alone, where literature documented that Minocycline, which has the reported adverse effect of hyperpigmentation, has structural similarity with Tigecycline [10]. On the other hand, during our observation period, none of our subjects is given IV Tigecycline or IV Minocycline, and darkening of skin is noticed in all subjects recruited.

Polymyxin B is renally excreted. Drug level found to be higher in paediatric population especially in infants could be due to functional immature of kidneys. Polymyxin B accumulates in the body thus could be the reason of darkening of skin being intensified at the end of treatment.

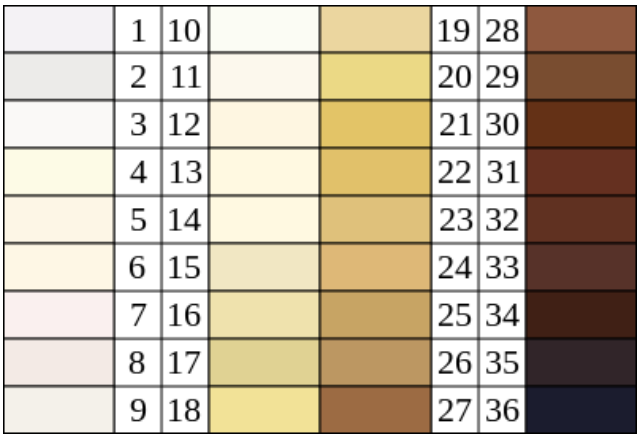
Besides, all concomitant antibiotics were assessed and none of them has been reported to cause hyperpigmentation. The concomitant antibiotics were Vancomycin, Amphotericin B, Cloxacillin, Ceftazidime, Amikacin, Meropenem and Metronidazole.

In addition, phototherapy is excluded as a main cause of generalised skin hyperpigmentation, as not all infants recruited were receiving phototherapy and IV Polymyxin B concurrently.

Conclusion

As a conclusion, this study shows that generalised skin hyperpigmentation is a common adverse effect noted in premature infants receiving polymyxin B treatment. The skin pigmentation of all the infants improved when the drug was discontinued. In our literature search, there has been no report on skin hyperpigmentation due to Polymyxin B. We are reporting this as additional adverse effect as the use of Polymyxin B is becoming prevalent. However, the exact pathogenesis of hyperpigmentation is still unknown. Larger sample size is needed to document the adverse reaction more evidently.

APPENDIX A



APPENDIX B

POLYMYXIN B INDUCED GENERALIZED SKIN HYPERPIGMENTATION IN INFANTS

Section 1

PATIENT DEMOGRAPHICS			
Name		**Gestation age (Weeks)**	
Gender		**Date of birth**	
Race		**Weight (kg)**	
ID number			

Section 2

Ward Medications			
	Duration		**Duration**

Section 3

Concomitant medications	

Section 4

Culture & Sensitivity Test					
Date (Sampling)	**Date (Reporting)**	**Source/ Sample**	**Mircoorganism**	**Sensitivity**	**Resistant**

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