



Echinocandin in an Intensive Care Unit: A Pearl's Peril in Intra Abdominal Post-Operative Care



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Abstract

Anidulafungin is an echinocandin armamentarium antifungal drug, indicated for use in invasive candidiasis [1]. The mechanism of action is by preventing the synthesis of fungal cell walls [2], However identification and initiation of treatment for invasive candidiasis is difficult and challenging for intensivists in a cohort of critically ill patients during post-operative period. To our knowledge this is the first documented case of such side effects associated with the use of Anidulafungin.

Introduction

During post-operative period, identification of fungal infection is challenging to diagnose. Most of the patients have multiple drains inserted during surgical procedures to facilitate drainage end up staying in-situ due to on-going risk of persisting intra-abdominal collection or fistula. In some elderly patients, surgeon prefer them to be left if the output from drain remains high as risk of opening abdomen is deemed far higher. In all these cases, despite use of

biomarkers like pro calcitonin and other investigations, it is down to clinicians to rule out fungal infections in acute setting mainly using his clinical acumen.

Anidulafungin is an Echinocandin antifungal drug, indicated for use in invasive candidiasis [1]. The mechanism of action is via the inhibition of beta-(1,3)-D-glucan synthase thereby, preventing the synthesis of fungal cell walls [2].

Case Summary

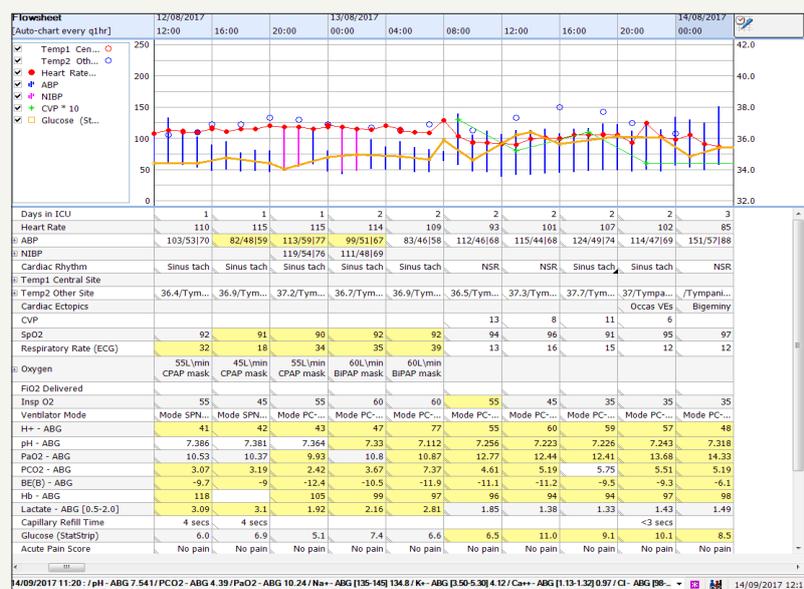


Figure 1: Flow sheet of the patient's daily vital observations, ventilation mode and arterial blood gas analysis etc demonstrating type1 respiratory failure with increasing FiO2 requirements on ITU.

A 58 years old lady presented to A&E with sudden onset, epigastric pain, associated with an episode of vomiting a few hours later. Her past medical history included hypertension and breast cancer, for which she underwent a lumpectomy. In addition, her regular medications included bendroflumethiazide, exemstone and loratadine. On examination, the patient was tachycardic with a rigid abdomen and generalised tenderness [3-5]. Both Cullen’s and Grey Turner’s signs were negative. Initial investigations revealed a serum amylase of 1400U/l, a lactate of 6.4(units) and CT scan

revealed severe interstitial pancreatitis of unknown aetiology. She was admitted to the surgical high dependency unit, where triple antibiotic therapy (metronidazole, gentamicin and meropenem), fluid resuscitation and non-invasive ventilation were commenced (Figure 1).

On day 3, the patient was admitted to ICU in view of a rising creatinine, procalcitonin and respiratory failure needing NIV. She had type 6 loose stool, a temperature of 36.4°C and was continued on the same antibiotic regime (Figure 2 & 3).



Figure 2: Flow sheet of the patient’s daily vital observations, ventilation mode and arterial blood gas analysis etc, demonstrates persistent rise in her body temperatures (pyrexia).

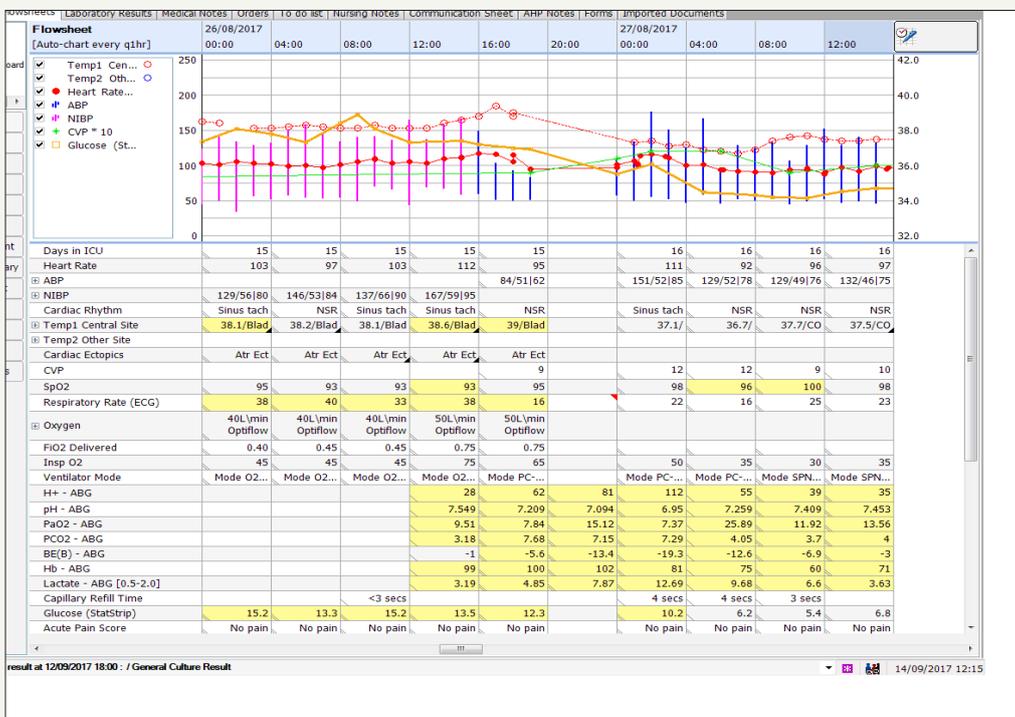


Figure 3: Flow sheet of the patient’s daily vital observations, ventilation mode and arterial blood gas analysis etc, demonstrates patient struggling with opt flow (High flow) oxygen after successful extubating heading to re-intubation and invasive ventilation. It also demonstrates incremental trends in glucose signalling complete loss of functioning beta cells of Pancreas.

On day 7, the patient deteriorated further, becoming pyrexial and requiring intubation due to respiratory failure. An anti-fungal, fluconazole, was commenced in addition to the antibiotics. Over the course of the next week, the patient showed improvement in inflammatory markers and was extubated, however, she remained pyrexial (Figure 4-7).

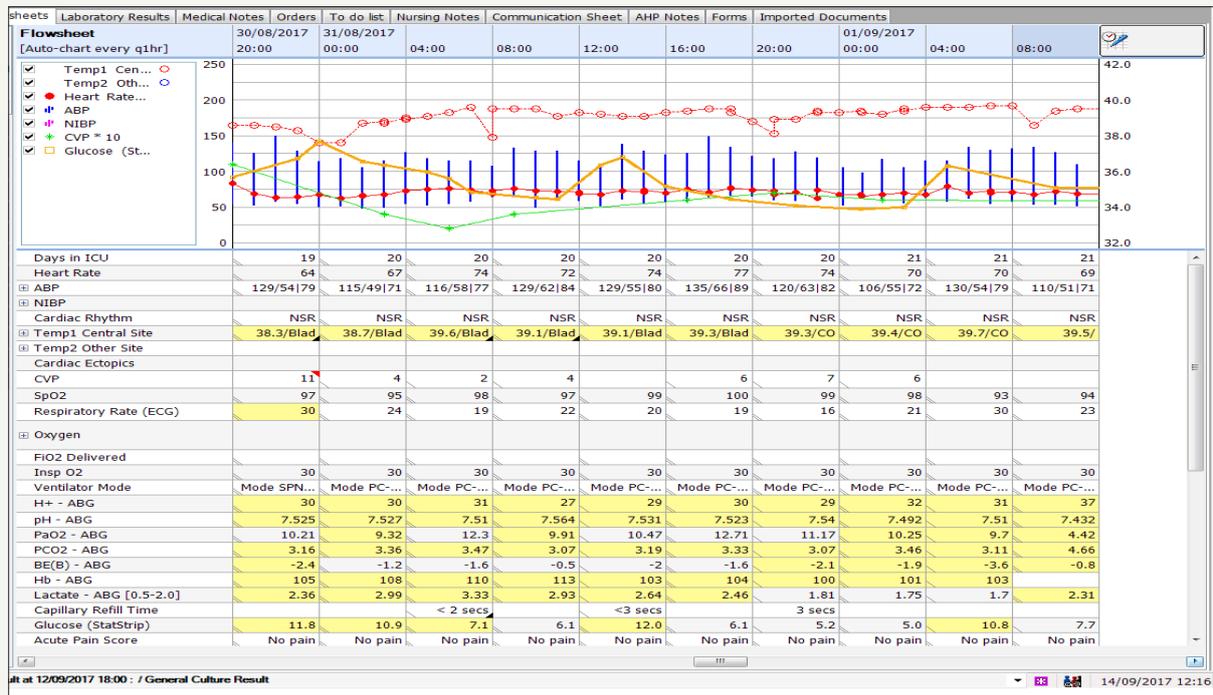


Figure 4: Flow sheet demonstrating persistent high grade pyrexia despite fluconazole and antimicrobial regime.

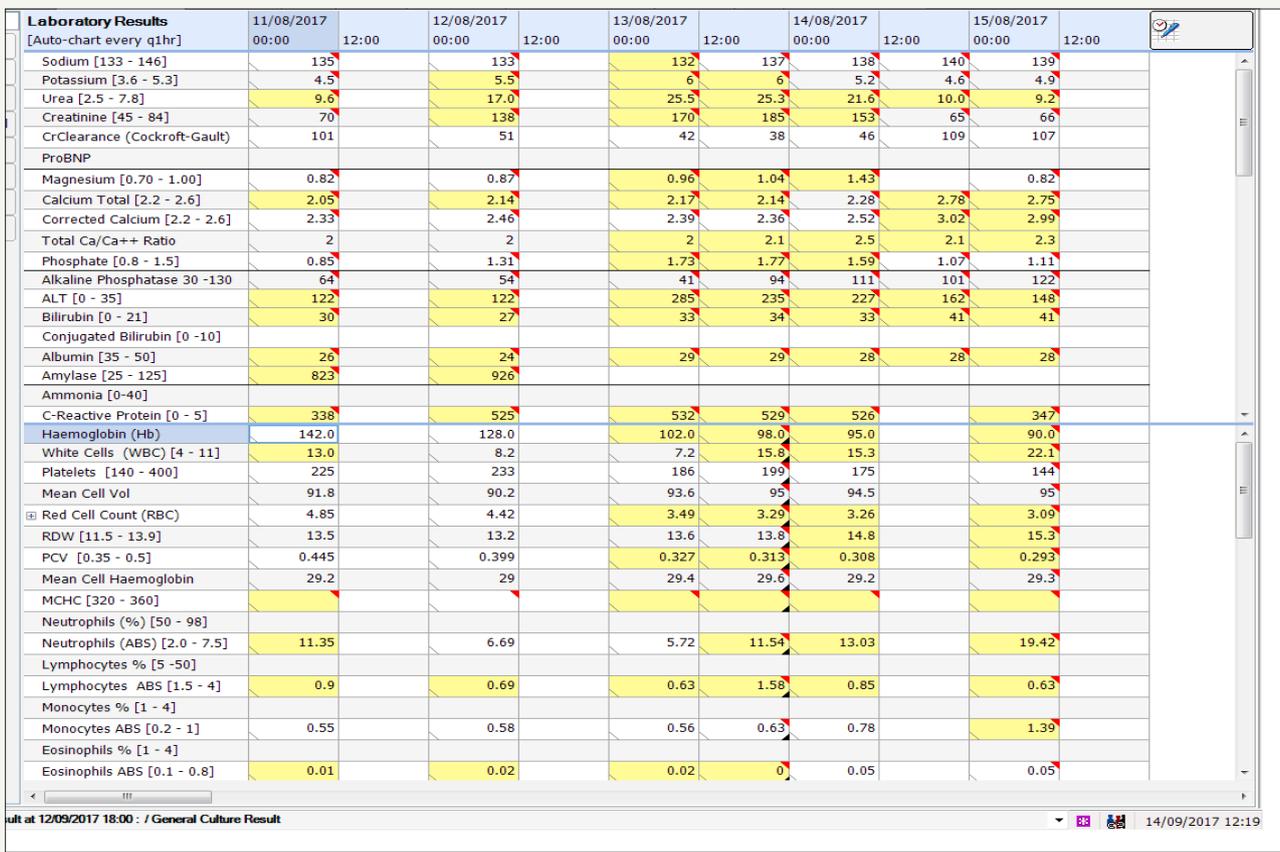


Figure 5: Flow sheet demonstrates the patient's septic showers.

sheets	Laboratory Results	Medical Notes	Orders	To do list	Nursing Notes	Communication Sheet	AHP Notes	Forms	Imported Documents	15/08/2017	16/08/2017	17/08/2017	18/08/2017	19/08/2017
Laboratory Results														
[Auto-chart every q1hr]														
	Sodium [133 - 146]		130		147		153		151		147		147	
	Potassium [3.6 - 5.3]		4.0		4.3		4.9		4.7		4.7		4.7	
	Urea [2.5 - 7.8]		9.2		14.5		17.3		16.6		14.6		14.6	
	Creatinine [45 - 84]		66		81		72		81		91		91	
	CrClearance (Cockcroft-Gault)		107		87		98		87		78		78	
ProBNP														
	Magnesium [0.70 - 1.00]		0.82		0.80		0.82		0.89		0.87		0.87	
	Calcium Total [2.2 - 2.6]		2.75		2.31		2.05		1.88		2.21		2.21	
	Corrected Calcium [2.2 - 2.6]		2.99		2.51		2.23		2.12		2.49		2.49	
	Total Ca/Ca++ Ratio		2.3		2.2		2		2.1		2		2	
	Phosphate [0.8 - 1.5]		1.11		0.36		1.25		0.89		1.29		1.29	
	Alkaline Phosphatase 30 -130		122		139		141		110		100		100	
	ALT [0 - 35]		148		97		65		46		35		35	
	Bilirubin [0 - 21]		41		31		23		19		26		26	
	Conjugated Bilirubin [0 -10]													
	Albumin [35 - 50]		28		30		31		28		26		26	
	Amylase [25 - 125]				45									
	Ammonia [0-40]													
	C-Reactive Protein [0 - 5]		347		226		124		79		71		71	
	Haemoglobin (Hb)		90.0		91.0		88.0		81.0		73.0		73.0	
	White Cells (WBC) [4 - 11]		22.1		20.4		20.9		13.9		17.0		17.0	
	Platelets [140 - 400]		144		151		214		355		403		403	
	Mean Cell Vol		95		91.5		94.2		94.9		96.4		96.4	
	Red Cell Count (RBC)		3.09		3.10		3.03		2.81		2.53		2.53	
	RDW [11.5 - 13.9]		15.3		14.6		16.7		16.3		17.5		17.5	
	PCV [0.35 - 0.5]		0.293		0.284		0.286		0.266		0.244		0.244	
	Mean Cell Haemoglobin		29.3		29.3		28.8		28.8		28.9		28.9	
	MCHC [320 - 360]													
	Neutrophils (%) [50 - 98]													
	Neutrophils (ABS) [2.0 - 7.5]		19.42		17.32		18.36		11.35		14.79		14.79	
	Lymphocytes % [5 -50]													
	Lymphocytes ABS [1.5 - 4]		0.63		1.17		0.88		1.32		1.1		1.1	
	Monocytes % [1 - 4]													
	Monocytes ABS [0.2 - 1]		1.39		1.18		0.86		0.72		0.65		0.65	
	Eosinophils % [1 - 4]													
	Eosinophils ABS [0.1 - 0.8]		0.05		0.03		0.02		0.03		0.01		0.01	

Figure 6: Flow sheet of the patient’s c-reactive protein, biochemistry and complete blood count reflecting septic process despite antimicrobial.

sheets	Laboratory Results	Medical Notes	Orders	To do list	Nursing Notes	Communication Sheet	AHP Notes	Forms	Imported Documents	19/08/2017	20/08/2017	21/08/2017	22/08/2017	23/08/2017
Laboratory Results														
[Auto-chart every q1hr]														
	Sodium [133 - 146]		147		151		150		148		147		147	
	Potassium [3.6 - 5.3]		4.7		4.3		4.2		4.9		4.4		4.4	
	Urea [2.5 - 7.8]		14.6		14.2		11.0		8.8		6.4		6.4	
	Creatinine [45 - 84]		91		84		75		69		53		53	
	CrClearance (Cockcroft-Gault)		78		84		94		103		134		134	
ProBNP														
	Magnesium [0.70 - 1.00]		0.87		0.91		0.87		0.91		0.90		0.90	
	Calcium Total [2.2 - 2.6]		2.21		2.00		1.83		1.77		1.84		1.84	
	Corrected Calcium [2.2 - 2.6]		2.49		2.32		2.17		2.17					
	Total Ca/Ca++ Ratio		2				1.9		1.8		1.8		1.8	
	Phosphate [0.8 - 1.5]		1.29		1.06		0.66		0.72		0.59		0.59	
	Alkaline Phosphatase 30 -130		100		107		104		89		79		79	
	ALT [0 - 35]		35		28		23		18		18		18	
	Bilirubin [0 - 21]		26		26		25		22		15		15	
	Conjugated Bilirubin [0 -10]													
	Albumin [35 - 50]		26		24		23		20		18		18	
	Amylase [25 - 125]													
	Ammonia [0-40]													
	C-Reactive Protein [0 - 5]		71		73		71		67		80		80	
	Haemoglobin (Hb)		73.0		82.0		78.0		86.0		85.0		85.0	
	White Cells (WBC) [4 - 11]		17.0		12.2		9.6		7.2		4.1		4.1	
	Platelets [140 - 400]		403		459		441		470		483		483	
	Mean Cell Vol		96.4		94.7		96.8		93.4		95.2		96	
	Red Cell Count (RBC)		2.53		2.82		2.69		3.07		2.89		2.89	
	RDW [11.5 - 13.9]		17.5		18.6		18.9		18.7		16.8		16.8	
	PCV [0.35 - 0.5]		0.244		0.267		0.261		0.286		0.277		0.277	
	Mean Cell Haemoglobin		28.9		29.1		28.9		28.8		29		29.5	
	MCHC [320 - 360]													
	Neutrophils (%) [50 - 98]													
	Neutrophils (ABS) [2.0 - 7.5]		14.79		10.44		8.11		8.56		5.77		2.97	
	Lymphocytes % [5 -50]													
	Lymphocytes ABS [1.5 - 4]		1.1		0.97		0.75		0.68		0.78		0.56	
	Monocytes % [1 - 4]													
	Monocytes ABS [0.2 - 1]		0.65		0.54		0.49		0.58		0.48		0.38	
	Eosinophils % [1 - 4]													
	Eosinophils ABS [0.1 - 0.8]		0.01		0.05		0.06		0.05		0.04		0.04	

Figure 7: Flow sheet of the patient’s white cell lineage trending after starting Andilufungin.

On day 18 the patient acutely deteriorated with an increased work of breathing followed by a drop in blood pressure. She had a semi-elective reintubation in view of her clinical deterioration and impending respiratory failure due to septic showers. A Computer tomography imaging revealed a perforated large bowel secondary to necrotizing pancreatitis requiring an emergency laparotomy with sub-total colectomy [6-8].

Fourth day post operatively, gentamicin was switched to vancomycin after staphylococcus epidermidis was grown from

Table 1: Results of the patient's white cell count (WCC), neutrophil count, lymphocyte count and monocyte from ICU admission onwards.

Day	CRP [0- 5]	WCC [4- 11]	Neutrophils [2.0- 7.5]	Lymphocytes [1.5- 4]	Monocytes [0.2 - 1]
3	338	13	11.35	0.9	0.55
4	525	8.2	6.69	0.69	0.58
5	532	7.2	5.72	0.63	0.56
6	526	15.3	13.03	0.85	0.78
7	347	22.1	19.42	0.63	1.39
8	226	20.4	17.32	1.17	1.18
9	124	20.9	18.36	0.88	0.86
10	79	13.9	11.35	1.32	0.72
11	71	17	14.79	1.1	0.65
12	73	12.2	10.44	0.97	0.54
13	71	10.1	8.56	0.68	0.58
14	67	7.2	5.77	0.78	0.48
15	80	4.1	2.97	0.56	0.38
16	61	2.4	1.67	0.43	0.2
17	87	3	1.93	0.63	0.26
18	292	5.2	4.24	0.51	0.29
19	140	17.3	14.7	0.27	1.83
20	284	19	16.85	1.02	0.92
21	307	16.7	14.56	1.18	0.67
22	176	21.5	14.67	5.31	0.84
23	143	18.2	15.62	1.72	0.67
24	81	18.6	16.53	1.09	0.51
25	60	13.8	12.08	1.08	0.51
26	30	12.5	10.96	0.86	0.47
27	20	5.5	4.41	0.66	0.32

the abdominal drain fluid. However, patient remained pyrexia and spiked high temperatures all throughout [9].

On day 26, Andilufungin was substituted in place of fluconazole. Patient stopped spiking temperature and clinically started to improve on day 27 (Figure 8). Interestingly, a marked drop in the patients' white cell lineage (WCC) was noted on day 29, specifically a lymphopenia and monocytopenia, which fell further over the next couple of days, with a neutropenia developing on day 31 (Table 1).

28	32	12.9	11.74	0.43	0.59
29	52	5.4	4.48	0.44	0.38
30	42	3.7	2.63	0.6	0.34
31	66	2.4	1.53	0.53	0.19
32	77	2.9	1.89	0.6	0.25
33	64	3.2	1.91	0.81	0.39
34	54	4.5	2.71	1.07	0.47
35	42	4.9	3.38	0.92	0.39
36	51	6.3	4.61	0.98	0.48

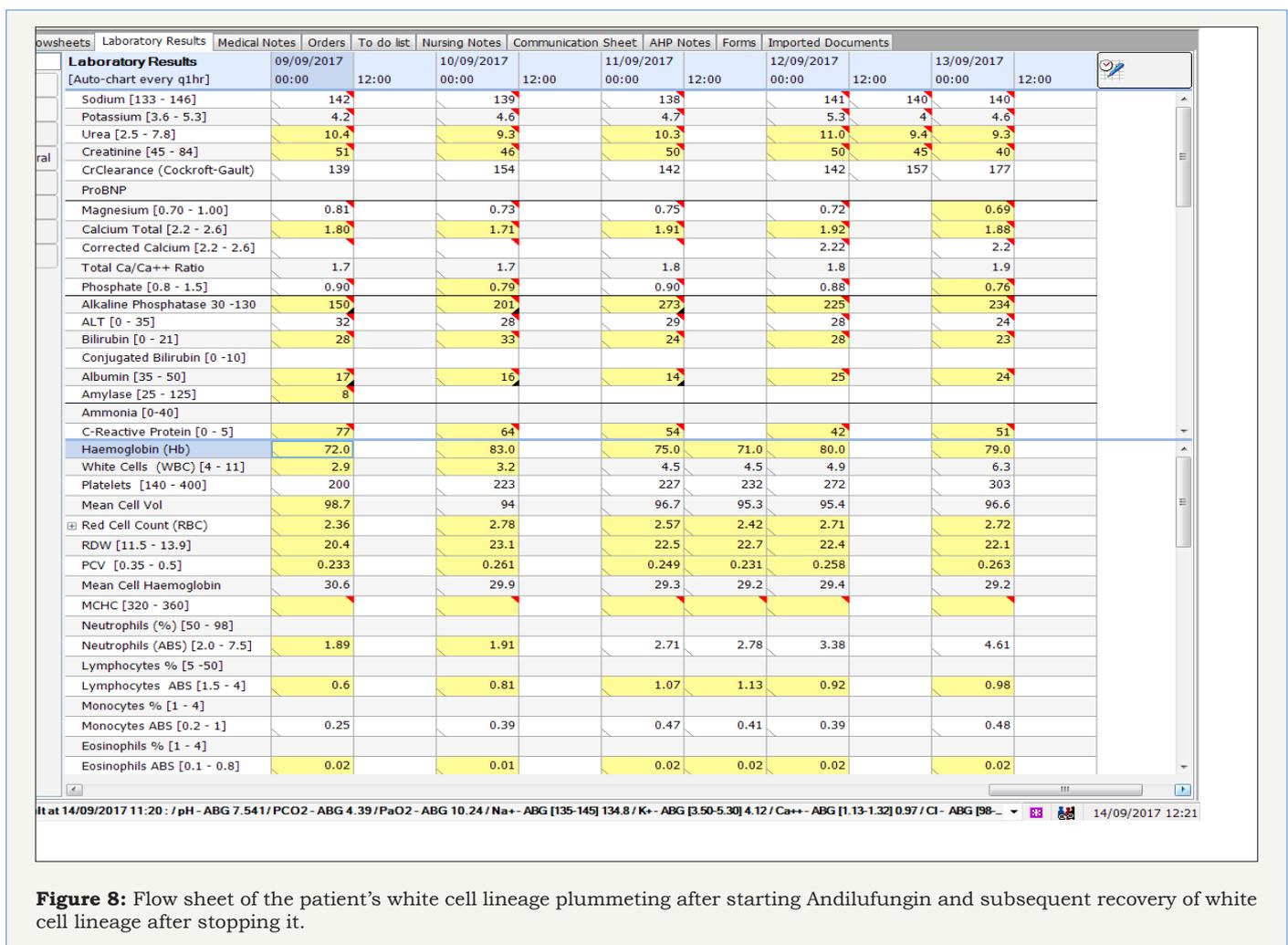


Figure 8: Flow sheet of the patient's white cell lineage plummeting after starting Andilufungin and subsequent recovery of white cell lineage after stopping it.

It was thought that the leucopenia was secondary to the antifungal. Andilufungin was stopped immediately after a multidisciplinary team meeting, whilst patient remained on meropenem, metronidazole and vancomycin [10]. The patient's WCC showed improvement within the next 24 hours and continued to stabilise over the following days.

Patient subsequently had to be started on caspofungin on advice of microbiologist (Figure 9). She developed critical illness myopathy. She had a tracheostomy and prolonged wean [11,12]. Patient was on total parental nutrition with complete bowel rest. She continued a slow recovery. She was subsequently referred to a tertiary small bowel transplant and dysfunction management centre (Figure 10).

Tests	Laboratory Results	Medical Notes	Orders	To do list	Nursing Notes	Communication Sheet	AHP Notes	Forms	Imported Documents
Laboratory Results	26/08/2017	27/08/2017	28/08/2017	29/08/2017	30/08/2017	31/08/2017			
[Auto-chart every q1hr]	12:00	00:00	12:00	00:00	12:00	00:00	12:00	00:00	12:00
Sodium [133 - 146]	138	140	141	142	142	141	144	142	145
Potassium [3.6 - 5.3]	7	6.1	5.6	5.1	5.1	5.8	5.4	6.6	5.8
Urea [2.5 - 7.8]	8.6	8.9	10.0	11.9	12.2	12.9	16.5	17.7	18.3
Creatinine [45 - 84]	93	113	101	77	65	66	73	82	73
CrClearance (Cockcroft-Gault)	76	63	70	92	109	107	97	86	97
ProBNP									
Magnesium [0.70 - 1.00]		0.70	0.67	0.80	0.81	0.87	0.87	0.84	0.90
Calcium Total [2.2 - 2.6]	2.31	2.10	2.19	2.11	1.99	1.88	1.74	1.75	1.71
Corrected Calcium [2.2 - 2.6]		2.5	2.49						
Total Ca/Ca++ Ratio	2	1.9	2	1.8	1.8	1.8	1.7	1.8	1.7
Phosphate [0.8 - 1.5]	2.57	2.09	1.82	1.42	1.24	1.41	1.17	1.44	1.14
Alkaline Phosphatase 30 - 130	63	57	80	122	154	172	216	257	222
ALT [0 - 35]	15	251	318	234	253	333	247	194	126
Bilirubin [0 - 21]	5	12	26	23	34	35	29	34	21
Conjugated Bilirubin [0 - 10]									
Albumin [35 - 50]	8	20	25	19	19	16	15	16	14
Amylase [25 - 125]									
Ammonia [0-40]									
C-Reactive Protein [0 - 5]	149	140	186	284	338	307	176	171	143
Haemoglobin (Hb)	101.0	72.0	70.0	70.0	113.0	112.0	106.0	108.0	108.0
White Cells (WBC) [4 - 11]	11.9	17.3	18.5	19.0	17.9	16.7	21.5	12.6	18.2
Platelets [140 - 400]	388	227	177	172	138	128	130	150	190
Mean Cell Vol	98.3	96.7	92.8	93.9	92	92.6	94.5	95.2	96.2
Red Cell Count (RBC)	3.39	2.49	2.46	2.37	3.83	3.76	3.56	3.63	3.67
RDW [11.5 - 13.9]	15.5	15.6	14.9	15.0	15.6	16.4	17.7	18.2	17.9
PCV [0.35 - 0.5]	0.333	0.241	0.228	0.223	0.352	0.348	0.336	0.346	0.353
Mean Cell Haemoglobin	29.7	28.9	28.7	29.4	29.5	29.7	29.8	29.8	29.6
MCHC [320 - 360]									
Neutrophils (%) [50 - 98]									
Neutrophils (ABS) [2.0 - 7.5]	7.44	14.70	16.39	16.85	15.73	14.56	14.67	11.46	15.42
Lymphocytes % [5 - 50]									
Lymphocytes ABS [1.5 - 4]	2.51	0.27	0.92	1.02	1.09	1.18	5.31	0.76	1.72
Monocytes % [1 - 4]									
Monocytes ABS [0.2 - 1]	1.51	1.83	0.83	0.92	0.74	0.67	0.84	0.25	0.67
Eosinophils % [1 - 4]									
Eosinophils ABS [0.1 - 0.8]	0.06	0.01	0.02	0.01	0.01	0	0.02	0	0

Figure 9: Flow sheet of the patient’s white cell lineage recovered completely after stopping Andilufungin, but patient needed caspofungin cover after 48 hours.

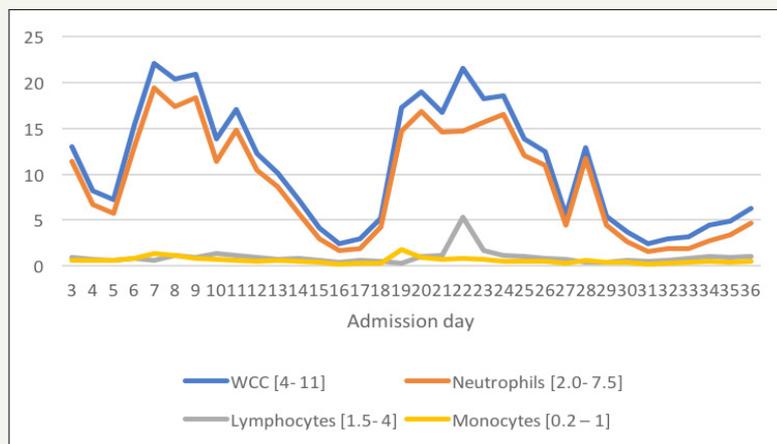


Figure 10: Results of the patient’s White Cell Count (WCC), neutrophil count, lymphocyte count and monocyte from ICU admission onwards, [normal reference ranges].

Conclusion

We present the case of a woman who developed selective bone marrow depression resulting in neutropenia, monocytopenia and lymphopenia after day five whilst on anidulafungin. To our knowledge this is the first documented case of such side effects associated with the use of anidulafungin. Clinicians should be aware the selective white cell lineage side effects, as it could result in significant risk of other infections in an already critically ill patient and risk prolonging their illness further especially in elderly patients.

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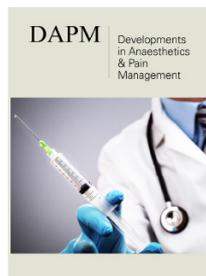
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