

Both Gram Positive and Gram Negative Organisms Complicate Neutropaenic Sepsis in Children with Leukemia. A Unit Audit Study and Recommendation

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Introduction

Neutropaenic sepsis is the most important cause of preventable mortality in children with cancer.¹ Early institution of empiric broad spectrum antibiotics is the cornerstone of childhood cancer therapy for the last 30 years and has reduced mortality attributed to sepsis from 30% to 1% currently.²

As we pursue increasing cure rates with more intensive multi-agent chemotherapy and the widespread use of long-term central venous catheters, breaches in the skin and mucosa together with prolonged severe neutropaenia actually increases the risks of neutropaenic sepsis. Fortunately, mortality from neutropaenic sepsis continues to decrease to very low levels of 1%. This is possible because of the constant review of the *current* bacteriological pattern in the treatment centre so that the appropriate empiric broad spectrum antibiotics can be instituted to adequately cover these organisms until blood culture and sensitivities come back.

Our choice of empiric antibiotics have changed over the years from ceftazidime/amikacin to the current ceftriaxone monotherapy. We conducted a retrospective audit study of the patients admitted with neutropaenic fever and their culture/sensitivity results to assess whether our current ceftriaxone monotherapy is sufficient.

Materials and Methods

This is a retrospective study of children with leukaemia admitted for neutropaenic fever over a 2-year period from January 2001 to January 2003. We collected data on demographic characteristics, disease status and the number of admissions for febrile neutropaenic episodes among children with leukaemia. A review of all cultures taken for the patients was done and microbiological laboratory results were collected to determine the pattern of organisms isolated.

Results

Twenty-eight children with leukaemia (Table I) were admitted for neutropaenic fever during the study period. The median number of

TABLE I: PATIENT CHARACTERISTICS

Characteristics	No. of patients
Total no. of patients	28
ALL	27
CML	1
Age (y)	
Median	5
Range	1½-14
Sex ratio	
Male: female	1.2:1
Disease status	
Remission	14
Relapse	14
No. of admissions for neutropaenic fever	
Median	4
Range	1-15

TABLE II: TYPE OF CULTURES TAKEN DURING FEBRILE NEUTROPAENIC EPISODES

Type of culture	No. of cultures	No. of positive cultures
Blood	213	32 (15%)
Wound	37	10 (27%)
Respiratory	14	2 (14%)
Urine	44	7 (16%)
Stool	30	3 (10%)

admissions for neutropaenic fever was 4 (range 1-15). There was an equal number of patients in remission and relapse (n = 14 each) with a slight male predominance (M:F 1.2:1.0). The median age was 5 years (range 1½-14 years). Majority of cultures taken during admission were from blood (n = 213) and other cultures were from urine (n = 44), wound/exit site (n = 37), stool (n = 30) and respiratory (n = 14).

Table II shows the overall positive cultures from the various sites. Fifteen percent of blood cultures yielded positive results. The highest positive yield came from cultures obtained from wound and central venous line exit sites (27%). Respiratory and stool cultures had only 14% and 10% culture positive results respectively.

Interestingly, there was a predominance of gram positive cocci infections (54%) compared with gram negative bacteria (46%) isolated in blood cultures. *Streptococci* spp was the single most common organism cultured in our patients, followed by *Staphylococcus aureus* and *Pseudomonas*. As expected, urine grew mostly gram negative microorganisms. Fungal microorganisms were uncommon but were the cause of death in 1 patient. Another patient died of multi-resistant *Pseudomonas aeruginosa* and progressive disease.

Discussion

Infection in the neutropaenic patient has remained a major preventable cause of mortality in cancer patients.¹ Institution of early empiric antibiotics during neutropaenic fever is one of the most important reasons for improvement in cure rates of childhood leukaemia over the last 30 years. Though there is a daunting list of possible types of organisms that can cause sepsis in an immunocompromised host, there is a recurrent pattern of organisms seen during the first days of presentation of neutropaenic fever.³ This reflects the pathogenic nature of such organisms and the breach in the skin and mucosa as the portal of entry for infections.

A constant audit of the pathogens cultured in each cancer unit is crucial in order to ensure that appropriate empiric antibiotics are used. With the widespread use of central lines and more intensive regimens that causes severe mucositis, there has been a shift from the previous predominance of gram negative sepsis to predominantly gram positive bacteraemia in this study.

Lee et al⁴ from our department studied 113 children with leukaemia from 1974-1984 and found that gram negative organisms accounted

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TABLE III: MICROORGANISM PATTERN AMONG POSITIVE CULTURES.

Type of cultures and microorganisms	No. of positive cultures
Blood cultures	26
Gram positive	14
<i>Streptococcus</i>	9
<i>Staphylococcus aureus</i>	4
<i>Gemella morbillorum</i>	1
Gram negative	12
<i>Pseudomonas</i>	4
<i>E. coli</i>	3
<i>Campylobacter</i>	1
<i>Enterobacter</i>	1
<i>Stenotrophomonas</i>	1
<i>Klebsiella/Pseudomonas</i> (mixed)	1
<i>Streptococcus/Klebsiella</i> (mixed)	1
Wound/exit site cultures	10
<i>Staphylococcus</i>	4
<i>Klebsiella</i>	2
<i>Pseudomonas</i>	2
<i>E.coli</i>	1
<i>Bacteroides</i>	1
Respiratory cultures	
<i>Candida/Aspergillus</i>	1
Urine cultures	6
<i>Pseudomonas</i>	2
<i>Proteus</i>	1
<i>E.coli</i>	1
<i>Klebsiella</i>	1
<i>Klebsiella/Pseudomonas</i>	1
Stool cultures	2
<i>Campylobacter</i>	1
<i>Clostridium</i>	1

for 53% (40/75) of episodes of bacteraemia. In this study in the same cohort of predominantly acute lymphoblastic leukaemia (ALL) patients, we found that gram negative organisms now account for only 46% of all bacteraemic episodes. There is a distinct shift in organism profile from gram negative organism to coagulase negative staphylococcus⁵ in 1992-1996 and now to streptococci in 2001-2003.

In addition, *Pseudomonas* sp has emerged to be the most common gram negative organism isolated (33% of gram negative organisms) in this study compared to the 1992-1996 cohort (18% of gram negative organisms isolated).⁵ This prompted us to change our empiric antibiotic of ceftriaxone monotherapy to ceftazidime/amikacin combination. Interestingly, *Streptococci* have now emerged to be the most important common pathogen (35% of all bacterial isolates and 64% of all gram positive isolates). Fortunately they are uniformly sensitive to penicillin, ceftriaxone and ceftazidime. The increasing importance of *Streptococci* may be from the presence of severe mucositis as a result of therapy. Fortunately we have not seen an increasing incidence of ARDS⁶ that results from these *Streptococci*.

Coagulase negative *Staphylococci* have decreased in importance as improved central line care has been instituted.⁷

Though it is intuitive that we institute the broadest spectrum and most powerful antibiotics in our armamentarium empirically so that most bacteria will be covered, this drastically increases treatment costs and worse still encourage development of resistant organisms. For example, our preliminary foray into using meropenem first line for some neutropaenic patients resulted in selection of multi-resistant *Sternotrophomonas maltophilia* in some patients. Moreover in the current era of disease-related group (DRG) coding and reimbursements, proper use of antibiotics through carefully audited culture results is crucial.

Conclusion

Blood cultures comprise a majority of cultures taken during febrile neutropaenic episodes. Among positive blood cultures, both gram positive and gram negative organisms are emerging as equally important pathogens and this should be considered in deciding for antimicrobial coverage. The increasing use of more intensive chemotherapy with its accompanying severe mucositis may increase the incidence of streptococci infections and should also be taken into consideration. Future studies should focus on increasing the yield in blood cultures to aid in the management of children with neutropaenic fever.

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Ambulatory Care of Central Venous Hickman's Catheters Can Be Successfully and Safely Carried out by Parents at Home: Results of a Patient Education Programme

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Introduction

Pain and vomiting are the usual images that haunt a child and family when they are told that the child is stricken with cancer. Pain, arising from the need to set IV plugs for chemotherapy and regular blood-taking for blood counts and chemistries, is probably one of the most stressful problems for children with cancer and their families. Though central venous lines ensure more reliable and safer administration of chemotherapeutic drugs by minimising extravasation that can cause severe skin necrosis, for children with cancer they are both a big blessing and their best friends. Central venous lines remove the need for painful needle sticks and free the child's hands to play, write and draw.

Hickman's catheters (HCs) are double lumen, cuffed, tunnelled central venous catheters frequently used in the care for children with cancer. Though HCs are welcome adjuncts to cancer care, they can create considerable morbidity and mortality if not used and cared for properly.^{1,2} Because HCs are externalised, they provide an easy route for bacteria to gain direct access into the bloodstream, causing septicaemia, infective endocarditis and even death. In addition, because it is a foreign body in the superior vena cava, it is prone to cause both thrombosis and embolism with dire consequences.

These are the reasons why HCs are managed with great caution by nurses. They require frequent aseptic cleansing, exit site skin care and flushing with heparinised saline at least twice a week. This entails added costs, inconvenience and repeated trips to the hospital by both the patient and parents/caregiver, as well as increased nursing burden for nurses.

In 1997, as part of our Home Care Programme and our aim to empower the patients and their parents to participate actively in their cancer care, we reviewed the standards of care for children with central venous lines and initiated the teaching of the basic principles of Hickman's line care to parents. This initially started as an unstructured discussion by nurses with parents and transferred the responsibility of home care for HCs to parents/caregivers. A year into the programme, we reviewed and showed that patients suffered a high rate of 11 infections per 1000 catheter days and required removal of many catheters.³ This led to a review of our Home Care Programme and the development of a systematic patient education programme for the training of caregivers, particularly parents, in the management of central venous line catheters at home. We describe our patient education programme for the home care of HCs in children with cancer and compared the incidence of infection sepsis in children with HCs before and after implementation of this programme.

Materials and Methods

Parents underwent a "Procedures Made Easy for Parents" Patient Education Programme conducted by nurses that emphasised simple

techniques on flushing HC and exit site dressings. A teaching plan was prepared with all the important aspects of each session clearly written out. Teaching aids were designed to ensure that a life-like demonstration can be carried out and a checklist was designed to track and monitor performance of nurses and parents/caregivers. Parents are guided until assessed to be capable and confident to conduct the procedures in front of the training nurse before they are allowed to administer care independently at home.

Subsequently, parents/caregivers performed skin care and flushing of HC by themselves at home, with regular home follow-up by the nurses who reviewed their techniques. Parents can call up for queries and come directly to the Paediatric Inpatient Cancer Centre if problems arise. A complete central patient database with central venous catheters was maintained and the complications tracked.

A retrospective study was done from January 1998 to October 2002 to determine the outcome of home care for HCs after the start of an intensive training programme. Data were collected encompassing demographic characteristics, underlying malignancy, neutrophil count on day of device insertion and presence of neutropaenia (absolute neutrophil count <1,000 cells/uL). A review of microbiology laboratory records was conducted to determine infectious complications. This included blood culture/exit site/catheter tip results and haematological parameters during admission. The outcome of therapy and reason for catheter removal were ascertained. The National Nosocomial Infection Surveillance System criteria for primary bloodstream infections were used to define bacteraemic episodes and bloodstream infection (BSI) rates were calculated by the number of BSI multiplied by 1,000 and divided by the number of HC days.⁴

Results

Forty children with cancer had a HC inserted from January 1998 to October 2002 during the implementation of the "Procedures Made Easy for Parents" Education Programme at our unit. Patients had a median age of 13.5 years (range 1-18) with male-to-female ratio of 3:2. 73% (n = 29) of these children had leukaemia and 27% (n = 11) had solid tumours; 33% (n = 13) of patients underwent stem cell transplantation. Parents cared for 30 (75%) patients with HC. The median duration of HC remaining *in situ* was 132.5 days (range 19-710) (Table I). The infection rate for HC was 2.41 per 1000 catheter days with relative risk for bloodstream infection at 2.13. Majority of infections were with gram negative bacteria, accounting for 1.7 bloodstream infections per 1,000 catheter days (Table II). Reasons for removal of HC include infection [10% (n = 4)], mechanical causes [5% (n = 2)], completion of therapy [48% (n = 19)] and mortality [33% (n = 13)]. Only 1 mortality was related primarily to sepsis. Two catheters were still in place at time of censor of follow-up.

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Discussion

Painful needle sticks are one of the most stressful problems confronting children with cancers. Central venous lines like HCs are welcome adjuncts to therapy minimising painful needle sticks and freeing the child's hands for play. However, HCs have a higher potential for infection due to its externalised position. Thus, HCs require frequent care which includes flushing, exit site care and changing the dressing twice a week.

Though, with proper Hickman's line care, the rate of infections can be greatly minimised to acceptable levels, this will require frequent trips to the hospital, which may be troublesome to parents and incur added cost to patients. Traditionally, nurses are singularly involved in the care of HCs. As more catheters are placed, increased burden is placed on the already heavy nursing loads.

In 1997, as part of our Home Care Programme and Total Cancer Care where parents are empowered to participate actively in their child's cancer care, we embarked on a parent-administered HC care at home. This was fraught with higher infection rates for HCs (11 per 1000 catheter days) compared to Porta-caths (3.1 per 1000 catheter days).³ Porta-caths do not require any home care compared to HCs.

The programme was redesigned to incorporate an intensive Parents Education Programme that involved comprehensive information for parents, teaching plan and aids, a performance checklist and close follow-up of parents/caregivers. Teaching aids that facilitated life-like demonstration, such as actual withdrawal of blood-like fluid

(red-coloured food dye mixed with water), were effective tools for learning.

We also procured a mannequin named Chester who has multiple detachable layers to illustrate how the HC works and how infections can be acquired. A practical demonstration is conducted that allows parents/caregivers to learn the techniques step by step and a checklist ensures that all areas of learning are covered. This is to guide the teacher throughout the session, thus increasing inter-teacher reliability. Once the parent/caregiver is deemed confident and competent, they are allowed to take care of the HC at home by themselves. Nurses conduct frequent home follow-ups to ensure adherence to technique and to deal with problems that may arise. In addition, parents/caregivers have direct 24-hours' access to the wards for questions via the telephone or can come directly to the Paediatric Inpatient Cancer Centre if any problems arise.

After implementation of this systematic "Procedures Made Easy for Parents" Patient Education Programme, we found that 75% (30/40) of catheters could be cared for by the parents/caregivers at home. The incidence of HC-related infections has been reduced from the historical 11 per 1000 catheter days³ to 2.41 per 1000 catheter days which is marginally higher than that for Porta-caths (0.85 per 1000 catheter days) during the same study period.

In our previous³ and current studies, we found that HCs have higher infection rates than Porta-caths. This is attributed to the fact that Hickman's lines are externalised and have 2 lumens, rather than a single lumen. If we adjust for the differences in lumen numbers, HCs have 1.2 infections per lumen per 1000 catheter days, which is minimally higher than Porta-caths (0.85) (Table III).

Conclusion

Majority of parents/caregivers can manage HCs with minimal risks of infection after an intensive educational programme. Our programme significantly reduces the inconvenience of repeated trips to the hospital without compromising catheter safety.

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TABLE I: SUMMARY OF PATIENT CHARACTERISTICS AND OUTCOME OF HCs

Characteristic	
Total no. of patients	40
No. of HC taken care by parents	30
Age (y)	
Median (range)	13.5 (1-18)
Sex (M:F)	3:2
Underlying diagnosis	
Haematological	29
Solid tumour	11
Bone marrow transplant	13
Neutrophil counts on day of insertion	
Median	2.46
Range	0.89-24.47
Neutropaenia	24
Site infection	0
HC removal	
2° to infection	4
2° mechanical causes	2
2° completion of therapy	19
2° mortality	13
Mortalities related to sepsis	1

TABLE II: BLOODSTREAM INFECTIONS CAUSED BY HC

Characteristic	
Duration of use (days)	
Total no. of days	7041
Median	132.5
Range	19-710
No. of BSIs	17
per 100 catheters	42.5
per 1,000 catheter days	2.41
No. of gram-negative BSIs	12
per 100 catheters	30
per 1,000 catheter days	1.70

BSI: bloodstream infection

TABLE III: COMPARISON OF CURRENT STUDY RESULTS WITH PRIOR PATIENT EDUCATION PROGRAMME

Study	Current		Huang et al ³	
	Hickman	Ports	Hickman	Ports
No of bloodstream infections				
Per 100 catheters	42.5	20	ND	ND
Per 1000 catheter days	2.41	0.85	11.0	3.1
Per lumen per 1000 catheter days	1.20	0.85	5.5	3.1

Pain Management at the Emergency Department—Can We Do Better?

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Introduction

The Emergency Department (ED) at Tan Tock Seng Hospital (TTSH) sees about 350 patients a day. It also received the highest number of ambulance cases amongst all the hospitals in Singapore. 15% of these cases present with a chief complaint of pain.

Our sequential approach to patient flow does not allow early intervention to deliver analgesia at the earliest possible time. A 2-week review of all cases presenting with pain to our ED showed that 55% of these patients received no analgesia. It was also found that the mean waiting time from registration to the time of administration of analgesia was 71.4 ± 45.7 minutes.

The aims of this study were:-

1. To study the perception of pain amongst patients by gender, age, race and type of injury;
2. To determine how the above factors affected decision by patient with regards to analgesia at triage; and
3. To determine the level of pain on the pain rating scale whereby patients would prefer analgesia to be given at the point of triage.

Materials and Methods

The study was conducted from 26 November to 7 December 2002. All patients presenting with pain secondary to minor injuries like abrasions, lacerations and contusions, and more severe injuries, like fractures and/or dislocations, were prospectively recruited. Patients were interviewed via a structured questionnaire.

Patients were asked to indicate on the Numeric Rating Scale (NRS) the pain they felt. They were then asked whether they wanted analgesia while they were waiting to be seen by the doctor and how long they thought was a reasonable time to wait before analgesia was given.

The patient's education level, occupation and financial background were also recorded. All doctors were blinded to the pain score as well as the answers to the study questionnaire. Records were later reviewed to see if patients received analgesia at the ED and how long it took before they received it. The results were analysed using SPSS for Windows 11.0.

Results

Of the 175 eligible patients, 167 patients agreed to participate while 8 declined. Of these 167 patients, 157 of them indicated their decision for analgesia at triage while 10 did not (69 wanted, 88 declined and 9 were unsure and 1 patient did not respond to the question). 54 (32.3%) patients were given analgesia while at the ED while 113 (67.7%) patients were not.

There were 130 (77.8%) male and 37 (22.2%) female patients. The median pain score was 6 (range 0-10) for both genders. No statistical significance in pain score ($p = 0.313$, Mann Whitney *U* test).

The mean age was 33.3 years (95% CI: 35.5 to 35.1). No significant correlation was found between the age of the patients and their pain score ($r = 0.075$, Spearman's correlation co-efficient).

There were 88 Chinese (52.6%), 14 Malays (8.4%), 37 Indians (22.1%) and 28 other races (16.7%). The Chinese, Malay, Indian and other races had a median pain score of 6 (range 0-10), 5 (range 3-10),

8 (range 1-10) and 6.5 (range 3-10) respectively. Indian patients had a significant higher median pain score when compared to the all other races ($p = 0.036$, Kruskal-Wallis test; adjusted)

No significant correlation was found between the NRS score of patients with different educational levels ($r = 0.004$, Spearman's correlation co-efficient) and financial background ($r = 0.053$, Spearman's correlation co-efficient)

There were 118 patients (70.7%) who suffered minor injuries and 44 patients (26.3%) who sustained fractures and/or dislocations. The median pain score was 6 (range 0-10) for those with minor injuries and also 6 (range 1-10) for those with fractures and/or dislocations. This was not statistically significant ($p = 0.99$, Mann Whitney *U* test). 5 (3%) of the cases had no indication of the nature of injury.

69 (41.3%) out of the 167 patients wanted analgesia at triage. Patients wanting analgesia had a median pain score of 7 (range 0-10) while those who declined had a median pain score of 5 (range 0-10). This difference was statistically significant ($p = 0.008$, Mann Whitney *U* test; adjusted).

The median pain score for patient's who received analgesia was 7 (range 3-10) while those who did not was 6 (range 0-10). This was statistically significant ($p = 0.01$, Mann Whitney *U* test; adjusted).

Amongst 69 patients wanting analgesia while waiting to be seen, 34 (49.3%) patients received analgesia while the remaining 35 (50.7%) did not. Of the 88 patients who declined analgesia while waiting to be seen, 20 (22.7%) patients received analgesia after consultation while 68 (77.3%) received no analgesia at all. This difference was statistically significant ($p = 0.022$, chi-square test; adjusted).

More Indian and "other races" patients indicated that they wanted analgesia at triage (Proportion wanting analgesia: Chinese = 30.2%, Malay = 50%, Indian = 63.6%, other = 62.5%; $p = 0.002$, chi-square test; adjusted) but this did not alter the proportions that subsequently received analgesia (Chinese = 30.7%, Malay = 28.6%, Malay = 28.6%, Indian = 37.8%, other = 32.1%; $p = 0.65$, chi-square test).

The gender, age and type of injury did not affect the patient's decision for analgesia (gender; $p = 0.45$, chi-square test, age; $p = 0.65$, unpaired t-test, type of injury; $p = 0.58$, chi-square test) or subsequent receipt of analgesia (gender; $p = 0.86$, chi-square test, age; $p = 0.69$, unpaired t-test, type of injury; $p = 0.35$, chi-square test).

The mean waiting time from arrival at the ED to the time patient received analgesia was 77.6 ± 43.2 minutes. Patients' expectations of waiting time for the delivery of analgesia did not change with their decision on whether they wanted analgesia at triage or not. 105 (66.7%) expected analgesia to be given within 15 minutes of their arrival at the ED.

Discussion

In our study, race had a significant effect on the median pain score. The proportion of Indian patients and patients of "other races" who wanted analgesia were also significantly higher. It was a common observation amongst our healthcare workers that patients from the Southern Asia region tend to have a lower threshold for pain

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compared to the other races. They are also more demonstrative of their painful experience and more inclined to want analgesia.

In our study, 69 (41.3%) patients indicated that they wanted analgesia while waiting to be seen by the doctor. However, only 34 (49.3%) received analgesia while the other 35 (50.7%) did not. The low analgesia prescription rate amongst those who indicated that they wanted analgesia is a cause of concern. We propagated that under treatment of pain could be due to no formal education in pain management and our current work processes. Hence, we need to inculcate in our staff the importance of pain management, and to understand the physiologic aspects of pain from the patients' perspective.

Our current work processes did not allow us to meet the patients' expectation of delivery of analgesia at the ED. The patients expected analgesia to be given within 15 minutes of their arrival at the ED. In a busy ED like ours, patients presenting with pain secondary to minor injuries, fractures and/or dislocations usually have a longer waiting time to be seen by a doctor as these injuries are not life threatening. While it is important for doctors and nurses to attend to life threatening conditions, it is also our duty to relief patient's pain at the earliest possible time.

The implementation of a protocol-based nurse delivery of analgesia and process evaluation are possible approaches to meet patient's expectation for the timely delivery of analgesia while not

compromising our care for patients with emergent life threatening conditions.

It is not possible to compare pain intensity between 2 individuals. One may assume that the intensity of trauma have an effect on the pain score. However, our study showed that intensity of trauma had no significant difference on the patient's pain score, preference for analgesia or subsequent receipt of analgesia. Pain is a subjective expression and can be affected by many factors like gender, age, race and psychosocial background. The pain score will act as a guide in stratifying patients in need of analgesia at triage.

Conclusion and Recommendation

We need to educate our healthcare workers on the importance of assessment and treatment of pain. The time to delivery of analgesia fell short of our patients' expectations. Our current workflow does not allow us to meet the patients' need and expectation for the timely delivery of analgesia. Therefore, it is important to improve our processes in the management of pain and to develop a protocol driven parenteral analgesia delivery mechanism whereby nurses are permitted to prescribe analgesia at triage. Assessing pain using the NRS is useful and this should be incorporated as the fifth vital sign in the assessment of all patients at triage. Patients with a pain score of 7 should be offered analgesia at triage and those with a pain score of 5 or less should only be given analgesia at triage if they requested for it.