THE NORTHERN HOSPITAL

FEBRILE NEUTROPENIA

"Bonaparte on the Bridge at Arcola, 17th of November, 1796", oil on canvas, Jean Antoine Gros

"They haven't seen anything yet…In our time, no one has the slightest conception of what is great. It is up to me to give them an example".

Napoleon Bonaparte, after the Battle of Lodi, May 1796

"From that moment, I foresaw what I might be. Already I felt the Earth flee from beneath me, as if I were being carried into the sky".

Napoleon Bonaparte, reflecting on the battle of Lodi,
Journal de Sainte-Helene 1815-1818

In 1796, France was in chaos, torn by internal revolution, beset by enemies on every side, it seemed on the brink of total anarchy. Yet somehow it seemed to have miraculously survived. The French conscript armies fought the professional European armies aligned against it with valour, but to "conventional wisdom" it seemed only a matter of time before defeat would come. Europe however was astonished and alarmed at the unexpected ferocity of the French defence. To the European powers arranged against them, Revolutionary France was an enemy like no other in history, and this was causing hesitation and confusion on the part of the allied generals. The French conscripted "citizen armies" on an industrial scale not previously seen in history, nor to be surpassed until the Great War. They fought for an ideal, the Revolution and the motherland, as opposed to fighting as a "job". Their citizen generals fought with new tactics, not previously seen, massed and coordinated artillery attacks were used to annihilate cavalry charges, which were a standard tactic since antiquity. Not only did this new breed of general use new tactics, however, they commonly fought along side their own troops!

In the winter of 1796 the most pressing attacks were coming from the combined armies of Piedmont and Austria in the South. The situation seemed desperate, however, countering the Austrians were a group of the very best of the new breed of French generals, a number of whom would later become "Marshals of France". Despite all the fearful odds against them and against all expectation, the governing Directory in Paris kept hearing reports of astonishing victories. The Directory understood well the power of propaganda to raise the spirits of the people of France, they wanted heroes to project to the people. They demanded detailed reports from the Southern front, and many were forthcoming. Reports came back of the heroic deeds of a number of their generals, but one name kept appearing above all others. This was of a certain very young commander of artillery. His name was Napoleon Bonaparte.

Two propaganda images from the Italian front were used by the Directory and later, the second of these in particular, to great effect by Napoleon himself. Both involved the heroic storming of bridges. The outcome of both battles depended on the quick thinking and quick action of the storming of a bridge before the enemy on the opposite bank could fully regroup to counter-attack. In both cases courage of the highest order was required. The first image came from the battle of Lodi, and a number of different versions of this incident appeared in paintings and prints. The French storm the bridge sustaining great numbers of casualties in the face of hellish cannon fire from the Austrians on the opposite bank. French commanders are usually seen in the foreground, but none are readily identifiable as individuals, rather it shows the collective heroism of the French citizen army as a whole. This image had a great effect on the morale of the people of Paris, but it would pale into insignificance when compared to the second image of bridge storming that would come just six months later. When compared to the battle of Lodi, the battle of Arcola was in reality a mere

skirmish, yet from it emerged one of the greatest iconic images of the age. The effect of this image on the people of Paris was not just inspiring it was electrifying and did more for the spirits of the people than did the more significant victory at Lodi.

The usefulness of propaganda was not lost on Napoleon. He took careful note of the heroic image of the storming of the bridge at Lodi and the inspiration it engendered in the rest of his troops. The Directory took note of the inspirational effect it took on the people of Paris. So when six moths later, a similar situation arose at the Arcola Bridge, one of Napoleon's leading generals Pierre Francois Augereau, whom he would in the future make a Grand Marshal of France, was ready. As the frightened troops hesitated at the bridge, Augereau rushed forward grabbed the French colours from the flag bearer and began to charge across the bridge, a few followed him but many were instantly killed and the group became pinned down. This was a pivotal moment in the battle. So impressed was Napoleon by Augereau's action, he then, to the horror of his staff, grabbed the fallen flag himself and charged across the bridge in person. According to Napoleon's aides-de-camp: "We suddenly saw him appear on the embankment, surrounded by his general staff, he dismounted withdrew his sword, took the flag and rushed onto to the middle of the bridge amidst a rain of fire. The troops saw him but none of them imitated him. I was present at that incredible cowardice and can hardly believe it…" Many of his personal staff followed him, and many were killed around him, but miraculously Napoleon himself escaped unharmed. Initially the troops held back too stunned at what they were witnessing, even the Austrians stopped firing momentarily when they thought a high ranking officer was approaching them for "negotiations". Finally a great throng of troops ashamed at their hesitance rushed the bridge in support of their commander. The throng became so great that in the confusion Napoleon himself was pushed into the river and would have drowned along with a number of others had not some of his men managed to drag him out of the water to safety. The battle was won; Napoleon had become an instant hero of the army and the fledgling Republic.

In Paris, the Directory realized it suddenly had the image they had been looking for. Not the collective this time, but rather of an individual, a hero whom the people would follow. A painter was sent to capture Napoleon's image of which those in Paris were almost completely ignorant. Initially Napoleon was reluctant but the young painter had come at the insistence of no less a person than his wife, Josephine. He somewhat reluctantly agreed to stay still for the portrait when the painter turned out to be Antoine-Jean Gros the leading pupil of no less than the great master of the age Jacques Louis David. Gros found him "cold and severe", unable to keep still. "One cannot give the name of sitting to the little time that he gives me", he complained in a letter to his mother, "I cannot therefore choose my colours; I have to resign myself to only painting the nature of his physiognomy, and after that, as best I can, to give the portrait its form". In fact to get him to cooperate it was said that Josephine playfully forced an impatient Napoleon to sit on her lap over breakfast while Gros in the background desperately scribbled out the sketches he needed to construct his painting. The result was "Bonaparte on the Bridge at Arcola" depicting a dashing young handsome hero and saviour of France. It instantly became one of the very greatest iconic images of the legend of Napoleon Bonaparte.

When we suspect a patient may have febrile neutropenia we must recall the image of Napoleon Bonaparte at Arcola. We must act immediately and decisively if the battle is to be won. These patients are in immediate danger of septic shock, they must be urgently triaged as category 2 and have antibiotics begun within 30 minutes of the suspected diagnosis.

FEBRILE NEUTROPENIA

Introduction

This condition is a true medical emergency.

Febrile neutropenia is generally defined as:

- Neutrophils less than **1.0×10^9 /L**

  (Less than 0.5×10^9 /L represents a *severe* neutropenia).

And

- Fever ≥38 ºC.

Urgent empirical IV therapy with broad-spectrum antimicrobials is required.

Note however that in the first instance the neutrophil count will not be known and febrile at risk groups must be assumed to be neutropenic in the first instance and treated, before results are available.

Febrile neutropenic patients (or those *suspected* to have this condition) should receive a national triage category of 2.

Antibiotic should be commenced within 30 minutes.

For specific considerations in children, see the RCH guidelines, (febrile neutropenia).

Pathology

Patients with neutropenia are at risk of acute overwhelming sepsis and septic shock and death.

The following groups are at particular risk:

1 Oncology patients:

- Including bone marrow transplant patients.

2 Patients on cytotoxic treatments:

- Immunosuppressive agents / radiotherapy / chemotherapy.

3 Immunosuppressed patients in general:

- HIV / AIDS in particular.

4. Other Drugs which may induce neutropenia:

- Clozapine, in particular

Clinical assessment

Any patient who presents with a **fever** and who **may** have **neutropenia due to immunosuppression**, (in particular those who are on chemotherapy or radiotherapy), should be considered as a case febrile neutropenia until proven otherwise.

Note that in the first instance the neutrophil count will not be known and febrile at risk groups must be assumed to be neutropenic in the first instance and treated, before results are available.

Antibiotics must be given in a timely manner, (within 30 minutes) - and not delayed by excessive investigation.

Note further that some septic patients, especially the elderly, may not show a fever, but if they appear unwell or show other signs consistent with sepsis, then they should also be treated as though a febrile neutropenic patient.

Assess whether the patient has any evidence for a source of infection, in particular consider:

- **Intravenous access lines**
- Chest
- Urine
- Cellulitis
- Overt or occult surgical sepsis
- Throat
- Peri-anal sepsis:
    - ♥ Note that patients with febrile neutropenia should **not** have PR examination.

Investigations

It should be noted that investigation results must not delay the initiation of antibiotics in cases of suspected febrile neutropenia.

The old adage of "shoot first, and ask questions later", although not a desirable one in most cases, more definitely applies in this scenario!

1. FBE:
    - Request urgent neutrophil count.
    - CRP
    - U&Es / glucose

- LFTS
- Blood cultures:
  - ♥ Ideally two sets taken from different peripheral veins.
  - ♥ If the patient has venous access lines:
    - ♥♥ 1 set should be taken from **each** lumen of the central venous access device, where this has more than one port.

2. CXR

3. Urine for M&C

Others as clinically indicated:

4. Throat swab / Nasopharyngeal swab for respiratory multiplex PCR

5. Sputum for M&C

6. Faecal M&C if diarrhoea, include testing for **Clostridium difficile.**

Management

Febrile neutropenic patients should receive a national triage category of 2.

Assessment is urgent and if febrile neutropenia is suspected broad spectrum antibiotic must be commenced within 30 minutes.

1. **ABC and initial resuscitation as clinically indicated.**

   If in septic shock, the aggressiveness of the resuscitation in oncology patients will depend on:

   - The fitness of the patient.
   - The curability of the underlying disease.
   - The iatrogenic nature of the presentation.
   - Patient/ carer wishes including any prior advanced medical treatment directives.

2. **Empiric antibiotics** *(within 30 minutes of arrival)*:

   If not systemically compromised (SBP $\leq$ 90 mmHg, RR $\geq$ 30 or SaO_2 < 90%, HR $\geq$ 130, Altered conscious state, Clinician concern) **give:**

   - Tazocin, (*piperacillin + tazobactam)* 4.0 + 0.5 gms (child: 100 + 12.5 mg/kg up to 4 + 0.5 grams) IV, 8-hourly

This is a combination agent consisting of piperacillin and tazobactam, (a beta lactamase inhibitor)

For full dosing and prescribing details, see Antibiotic Therapeutic Guidelines.

Note in particular dosage adjustments in renal failure.

- **Anti-staphylococcal cover:**

  Specific anti-staphylococcal cover is not usually given unless:

  - ♥ The patient is very unwell, (septic shock)
  - ♥ Is known to be colonized with MRSA
  - ♥ Has clinical evidence of catheter-related infection, (eg Hickmans catheters or PICC lines) or skin infection.

  Give:

  - ♥ Vancomycin 25mg/kg (to a maximum of 2 grams) IV 12 hourly.

    Subsequent dosing then depends on renal function - see Antibiotic Therapeutic Guidelines or local protocols.

If systemically compromised (SBP $\leq$ 90 mmHg, RR $\geq$ 30 or SaO_2 < 90%, HR $\geq$ 130, Altered conscious state, Clinician concern) **give:**

- Meropenem 1gram IV 8 hourly, (**see also Appendix 1 below**).

And

- Vancomycin 25 mg/kg (to a maximum of 2 grams) IV 12 hourly.

For full dosing and prescribing details, as well as alternative regimes, see latest edition of Antibiotic Therapeutic Guidelines or local protocols.

Note in dosage adjustments of drugs in renal failure.

In penicillin allergic patients:

For **non-life** threatening reactions give:

- Cefepime 2 grams IV 8 hourly
- Consider IV metronidazole if abdominal symptoms/peri-anal infection

For **life-threatening** penicillin or B-lactam anaphylactic reactions give:

- Ciprofloxacin 400 mg IV 12 hourly

And

- Vancomycin 25 mg/kg (to a maximum of 2 grams) IV 12 hourly.

And

- Consider IV metronidazole if abdominal symptoms/peri-anal infection

3. Specific considerations:

    - Clostridium difficle: IV metronidazole is used
    - VRE: IV teicoplanin is used

    These cases should be discussed with an ID Physician.

4. If indwelling vascular access lines are **obviously** infected, they will need to be removed.

Disposition:

Consultations:

The **oncology unit** must be notified early of all cases.

The following may also need to be consulted:

- ID physician
- Microbiology
- For patients who are being treated at another hospital their unit should be notified.
- If the patient appears very unwell then there should be early consultation with ICU.
- A *positive pressure* isolation room needs to be requested.

Appendix 1

The Carbapenems [1]

*Widespread use of **carbapenems** has now been linked with the increasing prevalence of infections due to methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE), multiresistant Gram-negative organisms and Clostridium difficile.*

***Imipenem**, **meropenem** and **doripenem** have wide activity against enteric Gram-negative rods and Pseudomonas aeruginosa, comparable to that of aminoglycosides, and excellent activity against anaerobes, including Bacteroides fragilis, and many Gram-positive organisms.*

Meropenem and imipenem have activity against Nocardia species. Carbapenems are inactive against Enterococcus faecium, MRSA, Mycoplasma, Chlamydia, Stenotrophomonas and some Pseudomonas species.

***Ertapenem** has a similar spectrum of activity to the other carbapenems, but has poor activity against P. aeruginosa, Enterococcus and Acinetobacter species.*

Due to inactivation by a renal dipeptidase, imipenem is formulated in combination with the dipeptidase inhibitor, cilastatin.

Meropenem attains better concentrations in the cerebrospinal fluid and has a lower incidence of seizures than imipenem.

Ertapenem is long acting and can be given once a day.

The carbapenems are inactivated by metallo–beta-lactamases, which have been reported in Gram-negative bacteria in Australia. These enzymes are on mobile genetic elements and can be transferred between different genera and species.

Carbapenems are important broad-spectrum drugs and their use should be reserved.

"The Battle of Lodi 10th May 1796", oil on canvas, Louis Lejeune (1775-1848), Château de Versailles.

References

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