THE NORTHERN HOSPITAL

PENICILLIN ALLERGY

Vicksburg under attack from Ironclad gunboats, on the Mississippi, during the siege of Vicksburg, 18 May - 4 July, 1863. (Still from Ken Burn's, "The Civil War", 1990).

Against the advice of his advisors, Lincoln reinstated Ulysses S. Grant to field command. (after detractors had accused him of taking too many casualties at Shiloh)

"I can't spare this man", Lincoln said, "he fights". 1000 miles to the west, Vicksburg, high on a bluff overlooking the Mississippi, remained Confederate.

"Vicksburg," Jefferson Davis said, is the nail that holds the South's two halves together.

That fall, Grant tried to take the heavily fortified city. He failed. The Confederacy was on the offensive over a one thousand mile front…

"Vicksburg is the key. The war can never be brought to a close until the key is in our pocket"
(Abraham Lincoln)

"A long line of high rugged irregular bluffs clearly cut against the sky, crowned with cannon, which peered ominously from embrasures to the right and left as far as the eye could see. That is Vicksburg!"
(Ulysses S Grant)

For two and a half months Ulysses S Grant doggedly attempted to dig or hack or float his army through the tangled bayous and seize the town of Vicksburg. Nothing worked. The press accused him of sloth and stupidity, hinted he was drinking again. Finally Grant decided on a daring plan. He would march down river through the swamps on the western side, cross below Vicksburg, and without hope of resupply or reinforcement, come up from behind and attack the city. By early May Grant had crossed the river.

"When this was effected I felt a degree of relief scarcely ever equaled since. I was now in the enemy's country with a river and the stronghold of Vicksburg between me and my base of supply, but I was on dry ground on the same side of the river with the enemy"
(Ulysses S Grant)

The men knew they were cut loose from their base, knew they were going to be dependent for supplies on a very tenuous supply line, but Grant himself gave them confidence. They believed Grant knew what he was doing. And one great encouragement for their believing that was quite often on the march whether at night or in the daytime, they'd be moving along a road or over a bridge and right beside the road would be Grant on his horse - a dust covered man on a dust covered horse saying, "Move on, close up". So they felt very much that he was personally in charge of their movement, and it gave an added confidence.
(Shelby Foote, Civil War Historian).

In three weeks, Grant's army cut off from all communication with the outside world, marched 180 miles, fought and won five battles at Port Gibson, Raymond, Jackson, Champion's Hill, and Big Black River, and finally surrounded Vicksburg itself, trapping 31,000 Confederates. On May 19th Grant tried to take the town by direct assault but was beaten back.

"May 19th: Thanks be to the great Ruler of the Universe Vicksburg is still safe. The first great assault has been most successfully repelled. All my fears in reference to taking the place by storm now vanished".
(Reverend William Lovelace Foster, Chaplain 35th Mississippi Volunteers)

Grant settled in for a siege, resolved he said, to "outcamp the enemy".

"It is such folly for them to waste their ammunition like that. How can they ever take a town that has such advantages for protection as this. We'll just burrow into these hills and let them batter away as hard as they please"
(Confederate Housewife)

On May 15th Jefferson Davis summoned General Lee to Richmond. Something had to be done about Grant. Davis wanted to send part of Lee's army to relieve Vicksburg. Lee was against it. He had a bolder plan. The Army of Northern Virginia should invade the North again, striking this time into Pennsylvania. Lee would attack Harrisburg and Philadelphia and force Grant north to defend Washington. With luck Washington itself might fall. It might even force Lincoln to sue for peace and recognize the Confederacy.

Davis agreed. Everything now hung on Vicksburg in the west and Pennsylvania in the east. As Grant pressed his siege at Vicksburg, Lee moved north….

A thousand miles to the west, Ulysses S. Grant's siege of the rebel stronghold at Vicksburg had gone on so long that Grant himself had taken to the bottle out of boredom…..

Every day since late May, U.S Grant's 200 Union guns had pounded Vicksburg from land, while Admiral David Porter's gunboats battered it from the river.

"They fire at the city, thinking that they will wear out the women and children and sick, and General Pemberton will be obliged to surrender the place on that account, but they little know the spirit of the Vicksburg women and children"
(Vicksburg Housewife)

Civilians dug caves in the yellow clay hillsides, some with several rooms fitted out with rugs and beds and chairs and staffed with slaves. But food ran low. The city's defenders were reduced to eating mules, horses, and dogs. The Vicksburg Gazette had to be printed on the back of flowered wallpaper. There was no more newsprint.

"We are utterly cut off from the world, surrounded by a circle of fire. The shower of shells goes on day and night. People do nothing but eat what they can get, sleep when they can, and dodge the shells"
(Dora Miller)

"It was living like plant roots", one woman said. Union troops began calling Vicksburg "Prairie Dog Town"

Finally, after 48 days of siege, on July 4th, the same day that Lee began his retreat from Gettysburg, 31,000 Confederates surrendered. Confederate general John C. Pemberton said it would be an act of "cruel inhumanity" to subject his men to the terrible ordeal any longer. "Besides", he added, "I am an Northern man. I know my people. I know we can get better terms from them on the 4th of July than on any other day of the year".

The Stars and Stripes was raised above the Vicksburg courthouse. At the celebration aboard Admiral Porter's flagship on the Mississippi, Grant was the only one who did not touch the wine offered him, but contented himself with a cigar.

"Grant is now deservedly the hero, belabored with praise by those who accused him a month ago of all the sins in the calendar and who next week will turn against him and so blows the popular breeze. Vox populi. Vox humbug!"
(William Tecumseh Sherman)….

The Confederacy was cut in two. The Mississippi had become a Union highway. "The father of waters", Lincoln said, again goes unvexed to the sea".

"We have lost the Mississippi, and our nation is divided, and there's not enough left to fight for."
(Vicksburg Resident)

The 4th of July would not be celebrated in Vicksburg again for 81 years.

David McCullough and Shelby Foote in Ken Burns', "The Civil War", 1990.

Once a patient develops a severe well documented allergy to penicillin, he or she is stuck with it for life. The human immune cells, like the citizens of Vicksburg, have very long memories indeed - when it comes to penicillin, they never forget!

"Civilians dug caves in the yellow clay hillsides…." Vicksburg July, 1863.

PENICILLIN ALLERGY

Introduction

If penicillin is administered to a *highly* allergic patient, fatal anaphylaxis can occur.

Unfortunately patients, with no understanding of what constitutes an allergic reaction, **very commonly**, self report "allergies", especially **penicillin allergies.**

Self-reporting of penicillin allergy is notoriously unreliable, with up to half of patients reporting vague or even unlikely histories of allergy. [3, 4]

This constitutes a significant public health risk as the prescribing of "second-line" antibiotics in lieu of penicillin confers:

- **Risk of harm to the patient (i.e not getting the best antibiotic for their condition)**
- **Increased cost to healthcare**
- **Selection pressure favouring multidrug-resistant organisms due to the administration of less effective agents.**

Formal testing of patients who self-report penicillin allergy reveals that a large majority have no demonstrable allergy. [3]

A careful history must always therefore be obtained to ascertain if the "allergy" was likely a true life-threatening **IgE mediated anaphylaxis** or **severe skin delayed hypersensitivity reaction** such as **DRESS** or **Stevens-Johnson syndrome / toxic epidermal necrolysis**

The traditionally, and often, reported incidence of 10% cross reactivity of cephalosporin hypersensitivity, is now known be greatly overestimated.

In *general* terms:

1. In **severe** penicillin allergy (e.g. anaphylaxis, bronchospasm, urticaria angioedema), avoid beta-lactam antibiotics:
    - Penicillins
    - Cephalosporins
    - Carbapenems
2. In non-severe penicillin allergy (e.g. mild rash) use with caution:
    - Cephalosporins

- Carbapenems

See also separate documents on:

- **Anaphylaxis (in Allergy folder)**
- **DRESS (in Dermatology folder)**
- **Stevens-Johnson syndrome / toxic epidermal necrolysis (in Dermatology folder)**

Epidemiology

Anaphylaxis is more likely with parenteral rather than oral administration of antibiotics.

For **penicillin**, anaphylaxis occurs at an estimated frequency of 1 - 4 cases per 10,000 courses.

Of genuine anaphylaxis cases around 10% are fatal without urgent treatment.

Self -reporting of penicillin allergy among patients is notoriously high.

One Australian Emergency Department based study by Marwood et al. 2017, demonstrated a significant reduction in apparent prevalence of penicillin allergy following testing, with 81% of the tested patients initially reporting an allergy able to safely tolerate an oral challenge of 250 mg amoxicillin! This study indicated that the prevalence of patients *falsely* reporting penicillin allergy in Australia is similar to those in studies performed overseas.[3]

Pathophysiology

Immunology:

Haptens bind with endogenous carrier proteins to form the "major" (90%) and "minor" (10%) determinants of the immune response.

Types of Immune reactions:

Antibiotic hypersensitivity in general can be considered in 3 groups:

1. IgE-mediated immediate hypersensitivity:

   While many reactions are labelled as "allergic", *true* **IgE-mediated immediate hypersensitivity** is characterised by the development of:

   - Urticaria

- Angioedema
- Bronchospasm
- Frank anaphylaxis (with objectively demonstrated hypotension, hypoxia or tryptase elevation)

The reaction usually within **1 -2 hours** of drug administration.

If there is delay > 2 hours, there is less likelihood that the reaction is IgE-mediated.

2. IgE-independent reactions:

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These are essentially **histamine reactions** rather than true IgE mediated allergy responses.

They involve the ***direct*** **release of vasoactive mediators** such as histamine

They may be ameliorated by:

- Prophylactic antihistamines
- Slowing of infusion rates.

Examples include:

- IV Vancomycin "red man syndrome".
- IV NAC
- IV Morphine
- IV Streptokinase (no longer in clinical use)

3. Delayed reactions:

These reactions are usually **T-cell** (*not* IgE) mediated.

They typically manifest as macular, papular, or morbilliform rashes occurring **several days** after commencement of antibiotic treatment.

They are more common than immediate reactions.

They may in fact be y caused by the underlying infection as well as its treatment!

Delayed reactions commonly occur in patients with intercurrent **Epstein-Barr virus** (especially combined with aminopenicillin treatment) or **HIV infection**, and

such reactions are often not reproducible with deliberate challenge when the patient is well.

Viral examthems are common in children. Delayed rashes, especially with aminopenicillins, are not strongly predictive of future reactions and repeat exposure to beta lactams is **not** necessarily contraindicated.

Patch testing is not recommended for these kinds reactions.

The only way to ascertain non-IgE mediated reactions is direct challenge under medical supervision.

A specific type of delayed reaction is so-called "**serum sickness**"

Serum sickness is characterized by:

- Vasculitic rashes
- Arthralgia/arthritis
- Lethargy/ malaise and other non-specific constitutional symptoms
- Fever (occasionally).
- Proteinuria (occasionally)

This response is triggered more commonly with:

- **Cefaclo**r (more so than other cephalosporins
- **Sulfonamides**
- **Anti-venoms**

The reaction typically commences **several days** after the onset of treatment.

Most of these reactions are relatively mild, however some delayed reactions are **serious** and **potentially life-threatening**. They include the drug-induced **skin** (and systemic) hypersensitivity reactions:

- **DRESS (See separate document in Dermatology folder)**
- **Stevens-Johnson syndrome/toxic epidermal necrolysis (See separate document in Dermatology folder)**

Risk factors:

Risk factors for the clinical expression of antibiotic allergy in general include: [1]

1. Previous exposure:

    - Which may have been *non-therapeutic* exposure such as in utero or through food products.

2. Age 20 - 49:

    - Children and the elderly appear to be at are at lower (though not zero) risk

3. Route of antibiotic administration:

    - Allergic reactions to penicillin occur more frequently following parenteral rather than oral administration.

Cross reactivity:

Semi synthetic penicillins such as ticarcillin and piperacillin contain the same nucleus as penicillin G. Sensitivity to these antibiotics can therefore be assessed by skin testing to penicillin as well as the parent drug.

Cephalosporins share a common beta-lactam ring with the penicillins but the degree of cross-reactivity is actually quite low. A figure of 10 % cross reactivity is traditionally quoted, but this is now known to be a gross overestimate.

One large study gives the overall cross reactivity between penicillins and cephalosporins in individuals who report a penicillin allergy as approximately 1% and, in those with a confirmed penicillin allergy, 2.55%. [5]

Further cross reactivity is much less likely with the later 3rd and 4th generation **cephalosporins** than it is with the earlier 1st and 2nd generation cephalosporins. [5]

Monobactams such as aztreonam may be safely administered to penicillin allergic subjects

Carbapenems such as imipenem represent a significant risk to penicillin-allergic patients and should be withheld from penicillin skin test-positive patients.

Clinical Assessment

The diagnosis of antibiotic allergy is **rarely** clear-cut.

It is often not clear whether the symptoms are due to the patient's underlying condition or to the treatment.

For example, rashes may be caused by the underlying infection or occur as a result of antibiotic allergy.

The problem becomes even more complicated when the patient is taking more than one drug.

Antibiotic hypersensitivity is usually diagnosed on the basis of clinical history, especially the timing of the reaction after antimicrobial use.

If the patient reports an allergy, specific details about the nature of the reaction, the timing, concurrent illnesses and drugs, and the outcome should be sought, documented and provided to a clinical immunology/allergy specialist.

Patients, with no clear understanding of what constitutes an allergic reaction, very commonly, self report allergies, especially penicillin allergies.

A **clear history** of an IgE-mediated reaction means the drug should be avoided, unless the patient can be shown to be no longer allergic by formal skin testing with validated reagents followed by confirmatory drug challenge, or it is introduced using a desensitisation protocol.

Investigations

Antibiotic hypersensitivity is usually diagnosed on the basis of clinical history, especially the timing of the reaction after antimicrobial use.

If the patient reports an allergy, specific details about the nature of the reaction, the timing, concurrent illnesses and drugs, and the outcome should be sought, documented and provided to the clinical immunology/allergy specialist.

There is no single test for antibiotic allergy.

A basic problem in diagnosing antibiotic allergy by immunological methods is the fact that most antibiotics are not complete antigens but rather **haptenic metabolites** of the parent drug coupled with a **carrier tissue protein**.

With the exception of penicillin, immunoreactive drug metabolites have rarely been identified.

The role of allergy testing is limited largely to **immediate (IgE-mediated) hypersensitivity.**

Skin testing:

The only validated skin testing approach involves the use of penicillin major and minor determinants (where available) in penicillin allergy.

It is important to note that negative reactions may be seen if performed several months or years after the event.

Amoxycillin side chain - specific immune reactions warrant specific amoxycillin skin testing.

Intradermal skin testing is difficult to do in children under 10 years of age.

Skin testing should only be performed by specialists due to the risk of anaphylaxis.

Most non-pruritic maculopapular rashes will not be predicted by skin testing.

Blood testing:

Tests include:

1. FBE:
    - For eosinophilia
2. LFTs:
    - For raised liver enzymes may indicate that a reaction is related to drug administration.

      Eosinophilia and/or abnormal liver function tests however are often due to T-cell / non-IgE-mediated reactions rather than IgE-mediated reactions.
3. Tryptase:
    - **Tryptase** elevation on a blood sample collected within 1 - 4 hours after a reaction is consistent with mast cell degranulation.
4. ImmunoCAP:
    - Blood allergy testing (ImmunoCAP) is available for penicillin G, penicillin V, amoxicillin and cefaclor through commercial laboratories and is most accurate when measured close to the time of the event.

It is important to note that results of allergy testing may become negative with time from the event, and that testing may be negative even in patients who have current allergy.

Thus, a negative test in the presence of a **convincing history** does *not guarantee* safe administration.

For IgE-mediated antibiotic allergy, antimicrobial introduction can be judiciously employed where skin and intradermal tests are negative, or in circumstances where history suggests a low risk and alternative drugs are clearly inferior.

This should only be done under medical supervision, after consultation with a clinical immunology/allergy specialist.

In these cases, the degree of suspicion surrounding possible life-threatening reactivity will dictate whether a desensitisation protocol is preferable to oral challenge.

Management

Prevention:

Avoidance:

Patients with known severe / life threatening hypersensitivity reactions should be strongly advised to wear a **medical bracelet** or **necklace** advising of their allergy.

A clear history of an **IgE-mediated reaction** means the drug should be avoided, unless the patient can be shown to be no longer allergic by:

- **Formal skin testing** with validated reagents followed by confirmatory drug challenge

Or

- It is introduced using a **formal desensitization protocol**.

Desensitization:

This should only be done by specialists in **Allergy medicine.**

Treatment:

Treatment of anaphylaxis is according to standard protocols (**see also Anaphylaxis in Allergy folder**).

The management of a patient who reports penicillin hypersensitivity, and in whom a penicillin antibiotic is indicated, depends on a range of factors.

These include:

1. How clear or reliable that history is.
    - Is there any reliable medical documentation in the notes?
2. Establishing the exact nature of the "allergic" reaction

    It is vital to exclude serious reactions such as:

    - Immediate **IgE type hypersensitivity** (i.e **anaphylactic**) reactions
    - Serious skin / systemic delayed reactions such as **DRESS** or **Stevens-Johnson syndrome/toxic epidermal necrolysis**

3. Reconsider clinical necessity for antibiotic therapy.

4. How seriously (or potentially) unwell the patient is (or may become)

5. Are there other suitable antibiotics that can be used instead of a penicillin related drug?

After consideration of these factors:

In *general* terms:

1. In **severe** penicillin allergy (e.g. anaphylaxis, bronchospasm, urticaria angioedema), **avoid** the following beta-lactam antibiotics:

    - Penicillins
    - Cephalosporins
    - Carbapenems

2. In **non**-severe penicillin allergy (e.g. mild rash) use with caution:

    - Cephalosporins
    - Carbapenems

Safe Alternative Agents:

Antibiotic groups considered safe for use in those with penicillin allergy include the following groups: [1]

1. Aztreonam (a monobactam)

2. Macrolides:

    - Azithromycin, clarithromycin, erythromycin, roxithromycin.

3. Fluoroquinolones:

    - Ciprofloxacin, norfloxacin, moxifloxacin

4. Lincosamides:

    - Clindamycin, lincomycin

5. Tetracyclines:

    - Doxycycline, minocycline

- Tigecycline (a **glycylcycline** antibiotic, derived from the tetracycline antibiotic minocycline).

6. Oxazolidinones:

   - Linezolid

7. Trimethoprim/sulfamethoxazole

8. Glycopeptide antibiotics:

   - Vancomycin, teicoplanin

Adrenaline autoinjectors:

Patients with drug allergy do not normally require an adrenaline autoinjector to be prescribed as known drug allergens can usually be successfully avoided.

However, patients with IgE-mediated drug allergy and serious non-IgE mediated drug allergy should be advised to wear medical identification jewellery.

Disposition:

Patients who claim penicillin allergy, without clear medical documentation for this may be referred for formal testing, and/ or subsequent desensitization therapy, to a **Clinical Allergy Specialist**.

References

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