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ARTERIAL BLOOD GAS ANALYSIS

General Principles

Normal ranges of various parameters in human arterial blood are pH (7.35-7.45), PaO₂ (80-100 mmHg), PaCO₂ (35-45 mmHg), SaO₂ (97-98%), BE (±2), HCO₃ (24±2 mEq/L). An ideal requisition form should include the ventilatory status/set up details of the patient, his body temperature, position, activity and Hb.

Ideally a glass syringe is employed since there is minimum diffusion of gases across it and the free movement of piston will help confirming the position of the needle in the artery. Anticoagulants most widely used are Na heparins in 1 : 1000 litre as the pH is almost close to the physiological range. However, it may interfere with serum Na⁺ levels in which case lithium heparin may be used.

Amount of heparin required is 50 u/ml of blood.

Sampling errors

Most often it is the air bubble which is incriminated. As atmospheric air PO₂ is 158 mm and PaCO₂ of 40 mmHg, there is exchange of gases between air and blood according to gradient which is proportional to duration of exposure. As a result, there is decrease in PaCO₂, increase in PaO₂ and an increase in pH.

A venous blood admixture constituting 1/10th of arterial blood will decrease PaO₂ by 25%. Excessive dilution with heparin will behave as an air bubble as heparin solution is equilibrated to atmospheric air, however pH hardly changes since heparin is acidic.

A sample should be analysed within 2 hrs. if iced, and within 20 min if not. In a sample stored at 37°C, the PaCO₂ increases by 5mmHg, pH decreases by 0.05 and PaO₂ decreases by 20 mmHg every hour.

Since the most actively metabolizing cell in blood is the leucocyte, precipitous fall in PaO₂ occurs when TLC is abnormally high. This is termed Leucocyte Larceny.

Blood gas classification

Classification of an arterial blood gas sample should be done in the following steps:

1. pH Classification

Acidemia when pH is <7.35, and alkalemia if >7.45, Acidemia can be classified as severe (<7.2), moderate (7.2-7.3) and mild (7.3-7.35). Similarly, alkalemia may be mild (7.45-7.5), moderate (7.5-7.55) and severe (>7.5).

2. PaCO₂ classification

Lung function is proportional to the pulmonary venous bicarbonate (H₂CO₃) concentration and the closest correlate of the latter in arterial blood is PaCO₂. (>45 hypercarbia; <35 hypocarbia)

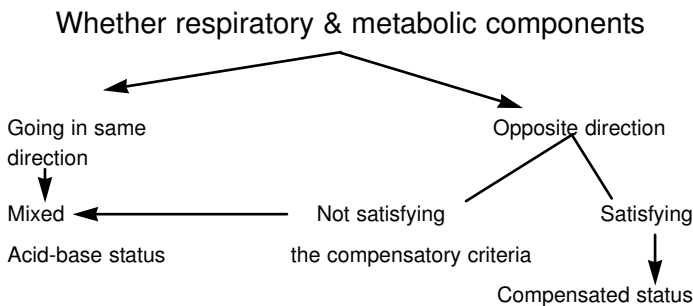
3. Metabolic classification

Metabolic parameters used are (HCO₃) and base excess (BE). It may indicate laboratory metabolic acidemia or alkalemia.

4. Assessment of Compensation

Compensation is defined as return of the abnormal pH to normal by a component that was not primarily involved.

The following flow chart indicates the procedure to assess for compensation:



Once a compensated status is identified, the primary and compensatory components should be identified. Primary component is one which is in the same direction of the pH since the body will never overcorrect by compensation. The compensation can be called well compensated if pH lies within the normal range, else it is poorly compensated.

As the renal compensatory mechanism is slower when compared to respiratory, the former can be called acute or chronic depending upon the degree

of compensation (Well compensated-Chronic; Partially-Acute).

Primary Component	Compensation	
	Primary	Secondary
Metabolic Acidosis	HCO ₃ ↓1.0 mEq/L	1.2
Metabolic Alkalemia	HCO ₃ ↑1.0 mEq/L	0.6
Respiratory Acidemia		
Acute	PaCO ₂ ↑10mgHg	1
Chronic	PaCO ₂ ↓10 mmHg	3
Respiratory Alkalemia		
Acute	PaCO ₂ ↓10 mmHg	2
Chronic	PaCO ₂ ↓10 mmHg	4

5. Final acid base classification

Accuracy check

Whenever there is external incongruence between sample results and clinical status of patient, a sampling or laboratory error should be suspected. Three methods are usually employed :

A. Indirect metabolic assessment

It relates pH with PaCO₂

$$\text{PaCO}_2 < 35; \text{pH} = 7.4 + (40 - \text{PaCO}_2) \times 0.01$$

$$\text{PaCO}_2 > 45; \text{pH} = 7.4 - (\text{PaCO}_2 - 40) \times 0.006$$

Accuracy limit of pH is + 0.03

B. Rule of 8

It relates pH, PaCO₂ and HCO₃.

Each pH is arranged as a factor. Predicted

$$\text{HCO}_3 = \text{Factor} \times \text{PaCO}_2$$

Accuracy of HCO₃ being ± 4mEq/L

pH	Factor
7.6	8/8
7.5	6/8
7.4	5/8
7.3	4/8
7.2	2.5/8
7.1	2/8

C. Modified Henderson Equation

It uses H⁺, PaCO₂, HCO₃

$$(\text{H}^+) \text{nEq/L} = \frac{24 \times \text{PaCO}_2}{(\text{HCO}_3)}$$

If two variables are known, the third can be determined.

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NEWER ANTIBIOTICS IN PULMONARY PRACTICE

I. Beta-lactam antibiotics

Mechanism of action : Binding of PBP (penicillin binding proteins) to bacterial cell wall causing lytic and non lytic killing of bacteria.

1. Ticarcillin : Carboxypenicillin. Serum half life of 1.2 hrs. Renal and hepatic excretion.

Spectrum of activity : Good activity against *Proteus vulgaris*, *Serratia* spp., and *P. aeruginosa*. Less active than penicillin G against Gram positive organisms.

2. Piperacillin : Ureidopenicillin. Half life of 0.8-1.5 hrs. Renal and hepatic excretion. Greater activity than carboxypenicillin against enterococci, *Bacteroides* spp., Gram negative organisms; *P. aeruginosa*, *Klebsiella* spp, *Serratia marscesens*, *E. coli*.

3. Combination with β -lactamase inhibitors

Ticarcillin + Clavulanic acid

Piperacillin + Tazobactam

Increases the activity against β -lactamase producing strains of *S. aureus*, *H. influenzae*, β . *fragilis* and *Moraxella catarrhalis*.

These combinations are not reasonable for serious infections caused by *P.aeruginosa* or nosocomial pneumonia, for which aminoglycoside should be coadministered.

Adverse effects

Anaphylaxis

Anaemia

Leucopenia

Interstitial nephritis

Bleeding (thrombocytopenia with ticarcillin)

II. Cephalosporins

Fourth generation - Cefipime and cefpirome

1. Cefipime

Serum half life 2 hrs.

Renal excretion

Spectrum of activity : Excellent activity against streptococcus, proteus, *E.Coli*, klebsiella, salmonella.

Very good activity against enterobacter, citrobacter, and *P.aeruginosa*. Moderate activity

against anaerobes. NOT active against MRSA, penicillin resistant pneumococci, enterococci, *B. fragilis*, and *L.monocytogenes*.

Indicated for empirical treatment of nosocomial infections.

2. Cefpodoxime Proxetil

Oral third generation cephalosporin.

Serum half life of 2.2 hrs.

Renal excretion.

Good activity against enterobacteriaceae, β -lactam producing *H.influenzae*, *M. catarrhalis*, and *S. aureus*.

III. Carbapenams

β -lactam structure but is unsaturated and has carbon atoms.

Mechanism of action : Binds to penicillin binding proteins and disrupts bacterial cell wall synthesis. Resistant to hydrolysis by most β -lactamases.

1. Imipenem

Serum half life of 1 hr. Renal excretion. Requires coadministration with cilastatin (renal dehydropeptidase inhibitor)

Spectrum of activity: Both gram positive aerobes and anaerobes. Very good activity against multidrug resistant *P.aeruginosa*, enterobacter, and citrobacter infections.

Adverse effects

Nausea and vomiting (1-20%)

Seizures (1.5%)

2. Meropenem

NOT sensitive to renal dipeptidase

Good activity against some imipenem resistant *P.aeruginosa*

Less active against gram positive cocci

3. Other drugs

Panipenem (sensitive to renal dipeptidase)

Oral agents : Lenapenem; faropenem

V. Trinems

1. Sanfetrinem (oral)

Serum half life 1.3-1.7 hrs.

Good activity against MSSA, penicillin and ampicillin sensitive *S.aureus*.

Excellent activity against *H.influenzae* and *M.catarrhalis*.

Moderate activity against *acinetobacter*.

NOT active against *P.aeruginosa* and *S.maltophilia*.

Good activity against anaerobes : β . *fragilis* and *peptostreptococcus*

2. Aztreonam

Monocyclic β -lactam

Serum half life of 1.7 hrs.

Renal excretion

Antimicrobial activity closely resembles aminoglycosides.

Excellent activity against Enterobacteriaceae family :

E. Coli, *Klebsiella*, *serratia*, *citrobacter* and *enterobacter* spp.

VI. Macrolides

Protein synthesis inhibitors

Mechanism of action

Inhibits protein synthesis by binding to blocking of elongation binding to 23s rRNA.

Drugs

Roxithromycin	Josamycin
Clarithromycin	Kitasamycin
Dirithromycin	Rosaramycin
Flurithromycin	Rokitamycin
Azithromycin	Miokamycin

1. **Clarithromycin** : Half life 4 hrs. Hepatic excretion.

2. **Azithromycin** : Azalide. Half life 68 hrs. Renal and hepatic excretion.

3. **Dirithromycin** : Half life of 30-44 hrs. Hepatic excretion.

Spectrum of activity

Good activity against Streptococci, Legionella, Mycoplasma, *C.pneumoniae*.

Clarithromycin and dirithromycin are more active against *H.influenzae* and *M.catarrhalis*.

Adverse effects

Low adverse effect profile of the currently

available antibiotics.

Nausea, vomiting, abdominal pain

Allergic reactions

Hepatotoxicity

Ototoxicity

Headache, dizziness

VII. Ketolides

14 membered ring macrolides where replacement of C-3 L-cladinose by a keto group are called ketolides.

Mechanism of action

Protein syntesis inhibitors. Higher affinity for unmehtylated ribosomes.

They do not induce resistance to macrolides or MLSb (Macrolide-lincosamide-streptogramin B) Resistance in *S.pneumoniae*.

Drugs

Telithromycin

HMR-3004

ABT-773

Telithromycin;

Serum half life of 13 hrs.

Hepatic and renal excretion.

VIII. Flouroquinolones

Mechanism of action

Inhibits DNA gyrase and topoisomerase IV.

Well absorbed orally; 70-90% bioavailability.

Serum half life of 4.7-18.7 hrs.

Renal and hepatic excretion.

Drugs

Gatifloxacin

Moxifloxacin

Gemifloxacin

Sparfloxacin

Levofloxacin

Sitafloxacin

Spectrum of activity

Excellent activity against aerobic gram negative bacilli including *E.Coli*, *klebsiella*, *enterobacter*, *citrobacter*, *P. mirabilis* and *P.aeruginosa*.

Good activity against staphylococci except MRSA.

For S.pneumoniae (penicillin sensitive)

Gemifloxacin>sitafloxacin>gatifloxacin>levofloxacin >ciprofloxacin.

For P.aueriginosa

Clinafloxacin>ciprofloxacin=sparfloxacin > gatifloxacin>levofloxacin

For S.aureus

Sitafloxacin = gemifloxacin > gatifloxacin > levofloxacin > ciprofloxacin.

For anaerobes

Sitafloxacin > gatifloxacin > trovafloxacin.

Adverse effects

- Nausea, vomiting, diarrhoea.
- Dizziness, headache.
- Phototoxicity.
- QTc prolongation.

VIII. Oxazolidinones

Linezolid

Early protein synthesis inhibitors.
Half life of 4-6 hrs.
Renal excretion.
Does NOT require renal modification
Spectrum of activity : Gram positive organisms; Staphylococci, streptococci, enterococci.
Gram positive anaerobic cocci; Corynebacterium, L.monocytogenes.

Mycobacterium is moderately susceptible.

Excellent activity against VRE, penicillin resistant strains of S. pneumoniae, Methicillin and vancomycin resistant intermediate strains of staphylococcus (VISA)

Adverse effects

- Nausea
- Diarrhoea
- Headache

IX. Streptogramins

Quinupristin/dalfopristin

Mechanism of action : Complexes with bacterial ribosomes to inhibit protein synthesis.

Spectrum of activity : Good activity against antibiotic resistant gram positive organisms, especially VRE, ORSA, VISA, and antibiotic resistant streptococci, pneumococci. Some activity against Moraxella, Haemophilus, and anaerobes.

In polymicrobial infections it should be combined with quinolones or cephalosporins for gram negative coverage.

SMALL-CELL LUNG CANCER (SCLC)

SCLC accounts for approximately 20% of all lung cancers in USA. It has the strongest association with cigarette smoking. Molecular studies have identified a consistent deletion of a portion of the short arm of chromosome 3 in most SCLCs. The 3p lesion is not unique to SCLC and has been noted in other non-pulmonary cancers (renal cell)

I. Etiology of Lung cancer

A. Tobacco

1. Tobacco (80-90%). Cigarette smoke causes damage to DNA in the bronchial epithelial cells
2. Dose-response relationship
3. Nicotine metabolites
4. 25% of lung cancers in non-smokers come from passive smoking
5. SCLC occurs exclusively in smokers

B. Other carcinogens

1. Asbestos
2. Radon daughters
3. Polycyclic hydrocarbons
4. Cadmium
5. Chloromethyl ethers
6. Chromium
7. Nickel
8. Inorganic arsenic
9. Air-pollution promotes action of other carcinogens

Factors that may decrease incidence of lung cancer

1. Vitamin A intake has shown to decrease the incidence of lung cancer especially in cigarette smokers

2. Beta-carotene?
3. Selenium

II. Genetic Factors and the Molecular Biology of Lung Cancer

- A. Activation of dominant cellular proto-oncogenes
- B. Inactivation of recessive or "tumor suppressor" genes
 - A. Dominant Oncogenes:
 1. Ras mutations seen in 35% of NSCLC; <2% in SCLC
 2. L-myc restriction fragment polymorphism seen in association with lung cancer
 - B. Recessive Oncogenes :
 1. Deletion in chromosome region 3p (14-23) in SCLC
 2. Retinoblastoma gene abnormality in SCLC
- C. Other genetic abnormalities:
 1. Abnormalities of p53 in SCLC
- D. Inherited predisposition to lung cancer

III. Pathology

Small cell lung cancer is divided into three pathologic subgroups: 1. Oat cell or small cell carcinoma (pure classical type), 2. Intermediate cell type (mixed small + large cell carcinoma), 3. Combined small cell + nonsmall cell carcinoma (~5%).

Many studies have shown that there are no significant clinical, therapeutic or prognostic differences between subtypes except the mixed cell variety which may have a lower response rate and a shorter median survival. It has neuroendocrine granules and is the cell type most commonly associated with peptide hormone secretions such as neuron-specific enolase, gastrin-releasing peptide (bombesin) and chromograin A. SCLC is also most commonly associated with ectopic production of hormones that cause paraneoplastic syndrome.

IV. Clinical Features

90% of lung cancers are symptomatic at the time of presentation

1. Local effects of the tumor: a. Central
 - b. Peripheral

2. Regional spread of tumor
3. Distant metastasis
4. Paraneoplastic syndromes

Paraneoplastic syndromes

1. Parathyroid like hormone secretion: Hypercalcemia, most common from NSCLC. If SCLC, consider mixed pattern
2. Hypertrophic pulmonary osteoarthropathy-often with adenocarcinoma (1-1%)
3. ADH secretion leading to SIADH (Syndrome of Inappropriate ADH). Most commonly associated with SCLC (5-10%); up to 50% may have subclinical SIADH (hyponatremia, increased excretion of sodium, normal volume, normal renal/adrenal function).
4. ACTH secretion : Most common lung cancer association with ectopic ACTH production is SCLC. 3-7% have Cushing's syndrome; up to 70% may have subclinical form.
5. Elevated calcitonin level in 38-67% of all patients with lung cancer, most commonly with SCLC. Causes calciuresis; usually not associated with symptoms.
6. Nephrotic syndrome, glomerulonephritis
7. Gynecomastia
8. Hypoglycemia (insulin like activity)
9. Hyperpigmentation (melanocyte-stimulating hormone)
10. Neuromyopathies: Most common with SCLC
11. Peripheral neuropathy: most common with SCLC; seen in almost 100% during the course of the disease.
12. Dementia: Most common with SCLC; treatment of SCLC may not result in improvement of dementia.
13. Subacute cerebellar degeneration; bilateral symmetric truncal and extremity ataxia; rapidly progressive in general. Most commonly with SCLC.
14. Eaton-Lambert syndrome: Similar to myasthenia gravis (MG), more pronounced weakness in lower extremities. EMG differentiates from MG.

Frequently improves with the treatment of the tumor.

V. Diagnosis

1. Imaging: Chest X-ray, CT chest
 2. Blood chemistries
 3. Sputum cytology
4. Bronchoscopy with bronchial and nodal biopsies

VI. Staging

TNM staging can be used for SCLC but the most commonly used staging is:

- a. Limited
- b. Extensive disease

a. Limited stage is defined as disease confined to one hemithorax and the ipsilateral supraclavicular nodes. The disease is encompassed within one radiation port.

b. Extensive disease is one that extends beyond the limited stage description.

(Disease that extends beyond ipsilateral hemithorax)

Staging work-up

1. Biopsy of mediastinal nodes
2. Biopsy of other sites if clinically indicated
3. MRI brain (15% positive at time of diagnosis, with 1/3 of these being asymptomatic)
4. CT abdomen
5. Bone scan/MRI bone (positive in 30% of patients without symptoms or elevated alkaline phosphatase)
6. Bone marrow biopsy - SCLC (low yield if LDH is normal)

History, physical examination, CXR, CBC, LFT, LDH, CT of chest to include liver and adrenals. CT/MRI head, bone scan depends on the clinical findings or protocol requirement. Routine bone marrow examination is not needed.

VII. Treatment of SCLC

Principles of SCLC treatment

1. SCLC is a systemic disease
2. Induction phase - definite
3. Maintenance phase - ? benefit. Not used in general

4. Combination chemotherapy is more effective than single agent therapy
5. A combination of radiation and chemotherapy has better survival for limited stage
6. Surgery for limited stage disease (Stage I or II) may be superior to chemo/radiation. MUST be done under research protocol
7. Prophylactic cranial radiation may be beneficial in limited stage disease

Limited - stage SCLC

One third of patients with SCLC have limited stage at initial diagnosis. This stage is highly responsive to therapy and 80-90% will have significant shrinkage of their tumor with chemotherapy and radiation. A complete clinical remission can be achieved in 50-60%. Median survival varies from 15-18 months, with a 2 year survival of 20-30% and 5 year survival of 10-15%.

The combined cisplatin and etoposide regimen was accepted as standard therapy in 1980s as they had increased survival and better response rates with low toxicity. From late 1980s based on studies, combined chemo and radiation treatment has been accepted as the standard of treatment as it shows increased survival compared to chemo alone. The chemo agents used are cisplatin + etoposide (CE) or CE alternating with CAV (cyclophosphamide, adriamycin and vincristine) at 3 week intervals. A total of 4-6 cycles in the duration of 4-5 months is given. No maintenance chemotherapy is indicated. Alternating regimens have been given to minimize the emergence of drug-resistance tumor cells but there is no consistent evidence of benefit. Salvage regimens are used in relapse.

Local tumor progression occurs in up to 80% with SCLC-limited stage. In limited disease, most centers use the addition of radiation to the chemotherapy on completion of chemotherapy (sequential therapy) for better survival. Recent studies show that concurrent use of chemo and radiation show median survival of 17-20 months with a 2 years survival of 40%.

The current best approach to chemotherapy is combined chemotherapy with concurrent radiotherapy. This modality has slightly increased toxicity but has increased survival benefit. There are ongoing clinical trials with hyperfractionation radiotherapy. The radiation therapy can be given as sequential to or concurrent or alternating with chemotherapy without changing chemo cycles.

- a. Etoposide + cisplatin + thoracic radiation
- b. Paclitaxel + carboplatin
- c. CAV - cyclophosphamide, doxorubicin and vincristine

Extensive Stage SCLC

Two thirds of all patients with SCLC will have extensive disease at the time of diagnosis. Response rate to chemo is 60-80%, with a median survival of 9-10 months and a 2-yr survival <10% and no 5 years survivors. Only 20-30% achieve complete remission with therapy. Chemo agents are similar to limited stage. The regimens include various combinations of cisplatin, etoposide, ifosamide, carboplatin.

New agents: Docetaxel, Vinorelbine, Gemcitabine, Topoisomerase I inhibitors (topotecan, irinotecan)

Prophylactic Cranial Irradiation (PCI)

PCI is a debated area of therapy in SCLC. Randomized trials have shown that PCI reduces the rate of brain metastasis but have not shown a survival advantage, and possible neurotoxicity. Recent two European trials have shown survival advantage and no significant neurologic sequelae. PCI remains controversial. If patient achieved complete remission in limited stage disease, one can choose to give PCI or closely follow up with CT or MRI of head at 3-4 month interval. If PCI is chosen, it should be given sequentially (not concurrently) with chemotherapy, total dose should be in the range of 30-36Gy and daily fraction sizes should not exceed 2.0 Gy

Role of surgery in SCLC

Nonrandomized trials and historical data have shown, in selected cases, 5 years survival rates of 25-35% with surgery, especially when SCLC

presents as solitary pulmonary nodule (SPNs). Solitary pulmonary nodule account for <5% of all cases of SCLC. Surgery is not a standard treatment for SCLC. It may be done in selected cases under a research protocol. The role of post-op chemotherapy in these patients is unclear. Even though, prolonged survival was noted in those who did not receive post-op chemotherapy, most investigators treat SCLC-SPN with adjuvant chemotherapy with established combination of drugs.

VIII. Prognosis

8% of all SCLC (10-15% of limited stage) survive beyond 5 years. Many of the patients who survive SCLC develop second primary lung cancer. Though highly responsive to chemo/radiation and most respond to treatment, the relapse rate within two years is high.

The median survival for limited stage is 14-20 months; for extensive disease 8-13 months; 20-40% of limited stage and less than 5% of extensive stage patients survive two years. At the time of diagnosis, brain metastases is seen in 10%, liver in 25%, bone metastases in 20%. Limited stage have a 2 years survival rate of about 30% while extensive stage has <10%. In limited stage, increases in LDH level are associated with reduced survival time. Median survival was 62 weeks if LDH was <193 units and 37 weeks if LDH was over 275 units. Normal leukocyte count and female sex are associated with more prolonged survival.

Adverse prognostic features

- a. Poor performance status and weight loss
- b. Limited versus extensive
- c. Elevated LDH
- d. Number of organs involved
- e. Metastasis to CNS, liver and marrow have poor prognosis
- f. Men do poorly compared to women.
- g. Presence of paraneoplastic syndrome is usually unfavorable.